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THE CARBON DIOXID AND OXYGEN CONTENT OF STOMACH GAS IN NORMAL PERSONS

ARTHUR D. DUNN, M.D., AND WARREN THOMPSON, M.D.

OMAHA

The complaint of eructations of gas, or "gas on the stomach," is so common that any contribution to the knowledge of the chemistry and source of stomach gas should be of interest. The subject has been studied more or less intensively from time to time, but a review of the literature shows that more accurate methods must be employed in its investigation in normal as well as in abnormal persons before knowledge of much clinical value is obtained. Most of the literature appears under the caption of aerophagia, and has to do with the nervous origin and treatment of the unpleasant symptom of gas belching, but does not deal with the composition of the gas. Toward the end of the nineteenth century impetus was given to the more serious investigation of stomach gas by the discovery of inflammable gases in the stomach in certain cases of pyloric obstruction, and an extensive literature arose on this subject alone; since that time the view has prevailed that except for air swallowed in food or saliva, and by "air swallowers," the chief sources of stomach gas are fermentation and putrefaction.

Planer,[1] in 1860, was apparently the first carefully to investigate gas occurring in the stomachs of normal men and animals (Fleischfresser). He maintained that carbon dioxid occurred exceptionally in the stomach, was constantly present in the intestine and that it was a product of fermentation. Planer's views were based largely on the examination of the gaseous contents of stomach and intestines in dogs recently killed, and prevailed until Schierbeck[2] reopened the subject in 1892. Schierbeck first repeated Planer's experiments and examined the gas found in human bodies immediately after death. Segments of the gastro-intestinal tract were tied off and removed, the gas collected over mercury and analyzed. He found that the carbon dioxid content rose as the anus was approached. In the stomach, carbon dioxid values of from 12 to 20 per cent. were obtained, and in the intestine values as

1. Planer: Sitzungsberichte d. Math.-Natur. Cl. d. K. Akad. d. Wissensch., Wien., 1860, quoted by Schierbeck.

2. Schierbeck, N. P.: Ueber Kohlensäure im Ventrikel, Skand. Arch. f. Physiol. **3**:437, 1892.

high as 50 per cent. were commonly present. He found nitrogen, some oxygen and a trace of hydrogen in stomach gas, while in intestinal gas there was much hydrogen and little oxygen. In animals he excluded regurgitation from the intestine as a possible source of stomach gas by tying off the pylorus. In order to obtain estimates in the living, he filled the stomach with water at various stages of digestion, drew off the water mixed with stomach contents and estimated the carbon dioxid by driving it off through boiling into a standard baryta solution. This method permitted of the determination of the carbon dioxid content at all stages of digestion. Shierbeck found that the tension of carbon dioxid varied from 30 to 40 mm. (3.9 to 5.3 per cent.) before eating, to 130 mm. (17.1 per cent.) two hours after ingestion of food. Schierbeck concluded that there was a definite increase of carbon dioxid in the stomach during digestion. He believed carbon dioxid to be a constant product of the cell activity of the gastric mucosa, and to be an expression of the carbon dioxid tension in these cells and not a factor of the concentration of carbon dioxid in the stomach wall, because he found the percentage of carbon dioxid greater during digestion. Schierbeck inferred that sodium bicarbonate and hydrochloric acid might even be secreted synchronously from the mucous membrane and coming together liberate carbon dioxid. Hoppe-Seyler [3] analyzed gas from twenty-two pathologic cases under varying conditions of disease and diet, and found carbon dioxid tensions varying from 3.2 per cent. in a case of post ulcer dilatation to 83 per cent. in a case of carcinoma of the stomach, and oxygen values varying from none to 17.02 per cent. in an "air swallower" without dilatation. Hoppe-Seyler stated that in doubtful cases an analysis should determine whether the gas is swallowed or comes from fermentation, indicating the clinical application of gas analysis to stomach disorders. He concluded that the carbon dioxid content was greater when free hydrochloric acid was absent (a conclusion exactly opposite to the one arrived at by Shierbeck), that frequently stomach gas consisted of air which had been swallowed, from which a portion of oxygen has been taken and carbon dioxid added, and that gas might find its way into the stomach from the duodenum. He attributed the origin of stomach gas largely to bacterial action, a view which figures widely in present day clinical beliefs. In 1912, Woodyatt and Graham [4] outlined clearly the problems involved in the subject of stomach gases, and studied three cases of acute dilatation of the stomach. In a case in which they gave the results of their analyses, no inflammable gas was found, 24 per cent. carbon dioxid,

3. Hoppe-Seyler, G.: Deutsch. Arch. f. klin. Med. **50**:82, 1892.
4. Woodyatt, R. T., and Graham, E. A.: Alimentary Respiration, Tr. Chicago Path. Soc. **8**:353, 1912.

4 per cent. oxygen and 72 per cent. nitrogen; fluid aspirated from the stomach produced no gas on incubation at 37 C. Woodyatt and Graham advanced the theory that in acute dilatation of the stomach there was a lack of available oxygen in the tissues with edema, hemorrhagic or serous exudation into the stomach, and impaired muscular tone; they concluded that "the distension of the stomach is a consequence of the gas evolution in a stomach whose wall is already crippled, atonic and unable to expel gas. The gas comes at least in part from the stomach wall, either directly or as a result of the action of the gastric juice on the carbonates of the exudate." Room air was introduced by them into the normal stomach, withdrawn in five minutes for analysis. They were convinced that the gastric mucosa had the power of liberating carbon dioxid.

Kantor,[5] in 1918, gave an extensive review of the literature and performed a few preliminary gas estimations on an unselected series of persons, aspirated at various intervals after eating. The average of five analyses gave carbon dioxid, 4.1 per cent.; oxygen, 17.2 per cent.; nitrogen, 79 per cent. The carbon dioxid values varied from 2 to 6.2 per cent.

It is apparent from the literature that carbon dioxid is the one gas constantly present in the stomach, and that carbon dioxid usually occurs in excess of the amount found in atmospheric air. Therefore, it was thought that a quantitative study of the carbon dioxid content of stomach gas in normal persons, under varying conditions, might throw some light on the origin of this gas, a subject in regard to which there seemed to be no unanimity of opinion, and also be of value as a preliminary to the quantitative study of stomach gas in disease. Obviously, there can be but three possible sources for this excess of carbon dioxid, viz.: (1) Secretion or diffusion of carbon dioxid from the stomach wall; (2) production of carbon dioxid from the food contents by bacterial fermentation; (3) regurgitation of duodenal contents into the stomach, which seems an unlikely source, as Schierbeck found the same carbon dioxid values, whether the pylorus was occluded or open. We decided, after a few preliminary analyses in patients complaining of "gas on the stomach," to confine our observations for the present to normals, as we had no basis for the estimation of abnormal variations, and to approach the problem in the following manner: first, to make careful quantitative determination of the carbon dioxid and oxygen content of gas obtained from the fasting stomach; second, to determine the changes occurring in the carbon dioxid and oxygen content in atmospheric air introduced into the fasting stomach;

5. Kantor, J. L.: A Study of the Atmospheric Air in the Upper Digestive Tract, Am. J. M. Sc. **155**:829, 1918.

third, to ascertain whether appreciable differences occurred in atmospheric air introduced into the stomachs of the same individuals, both when fasting and after a full meal; and finally, to ascertain whether gas was formed by incubation of stomach contents, and if so, under what conditions.

In order to learn to what extent carbon dioxid was present in the fasting stomach, the following method was used: To a T tube were attached a duodenal tube, a sampling tube and a Luer syringe filled with tap water. The air in the system was displaced as far as possible by water from the syringe, the syringe left attached, and the duodenal tube swallowed. When the duodenal bucket reached the stomach, the water was aspirated from the system by the syringe, the rubber attachment to this arm was clamped with a pinch cock, and the gas collected over mercury in a sampling tube. Analyses of four samples thus obtained from fasting stomachs were made with a standard Haldane gas apparatus and gave the following results:

TABLE 1.—Analysis of Samples Obtained at 8 a. m. from Fasting Stomach

Number	Carbon Dioxid	Oxygen	Nitrogen (by difference)
1	7.26	16.30	76.44
2	4.67	15.10	80.23
3	8.68	15.93	75.39
4	6.68	16.40	76.79

It was found that satisfactory samples of gas could be obtained in only two out of nine persons on whom the attempt was made. Fluoroscopic study of the fasting, as well as of the food containing stomach, showed that gas bubbles of sufficient size to furnish 50 c.c. of gas were the exception rather than the rule. Rough estimates made from fifty unselected roentgenograms gave the average size of the bubble as approximately 50 c.c. Even though sufficiently large, the gas bubble was often so placed that the duodenal bucket, because of its tendency to follow the gutter of the lesser curvature, could not be made to tap it; furthermore, in the majority of persons examined with the fluoroscope in the sitting or standing position, the gas bubble was found to be at a higher level than the cardiac inlet. The introduction of a fixed quantity of atmospheric air into the stomach would obviate difficulties in sampling. Besides, there is usually a certain amount of air in the stomach which has been swallowed with the food or saliva. Therefore, atmospheric air must, as a rule, enter into any gas mixture found in the stomach, and the introduction of a given amount of room air into the fasting stomach would merely supply the normal gas body, minus food and saliva. In the case of the fasting stomach, analyses of samples of gas taken at varying intervals after the introduction of atmospheric air

into the stomach would show whether carbon dioxid was secreted into the stomach, and if so, to what degree and at what rate. The method used was as follows: A duodenal tube was introduced into the stomach and 300 c.c. of air was injected into the stomach, the patient instructed to avoid belching or swallowing as much as possible, the tube clamped and left in situ, and samples taken at varying intervals. The analysis of ten samples, taken from twenty to thirty minutes after the introduction of 300 c.c. of room air into the stomach gave carbon dioxid, 5.26 per cent.; oxygen, 17 per cent. The results of two additional experiments on successive days in the same subject, with sampling at fixed intervals are shown in Table 2. It is noteworthy that in the same individual on successive days, under exactly similar conditions, an average variation of more than 1 per cent. occurred in the carbon dioxid and 0.5 per cent. in oxygen. Inasmuch as the main body of stomach gas following the ingestion of food is obviously swallowed atmospheric air, the determination of the changes that might occur in air injected into the fasting stomach was particularly pertinent in an effort to determine the normal gas content and its sources.

TABLE 2.—CHANGES THAT MIGHT OCCUR WHEN AIR IS INJECTED INTO THE FASTING STOMACH

Experiment	Room Air Injected	10 Minutes		20 Minutes		35 Minutes		50 Minutes		Average	
		Carbon Dioxid	Oxygen	Carbon Dioxid	Oxygen	Carbon Dioxid	Oxygen	Carbon Dioxid	Oxygen	Carbon Dioxid	Oxygen
No. 1	300 c.c.	1.8	19.3	8.1	16.9	5.9	17.5	4.1	17.1	4.98	17.7
No. 2	300 c.c.	0.2	21.6	2.9	18.0	6.3	16.7	6.4	16.5	3.95	18.2

Time denotes the interval between the introduction of room air into the fasting stomach and the taking of the sample.

In order to ascertain what influence the presence of food might have upon the relative gas values at stated intervals, 300 c.c. of room air were injected into the stomach of normal persons at varying periods of time after an ordinary breakfast. Controlled analyses of samples from the same persons while fasting were also made. The results of this series of experiments are given in Table 3. It is apparent from a study of Table 3 that the rate and degree of liberation of carbon dioxid does not depend on the presence of food in the stomach in normals. In Experiment 1 the average amount of carbon dioxid obtained was practically the same in the fasting and in the full stomach; in Experiment 2 the average amount of carbon dioxid was 0.92 per cent. greater in the fasting stomach; in Experiment 3, 0.90 per cent. greater in the digesting stomach; in Experiment 4 the average was 6 per cent. carbon dioxid in the fasting stomach and 4.8 per cent. after food. This is at variance with Schierbeck's observations, who found that the carbon dioxid tension paralleled the acidity. His carbon dioxid estimates were

made by driving the carbon dioxid by boiling from stomach contents which were obtained by washing with water. Boiling acidulated stomach contents releases the carbon dioxid from the food carbonates, and would account for the greater carbon dioxid values that he found in the presence of hydrochloric acid. An Ewald test breakfast acidulated to a normal free hydrochloric acid content will liberate from four to five volume per cent. carbon dioxid. The same carbon dioxid values obtain whether the test breakfast is acidulated in the stomach by its secretion or in vitro with hydrochloric acid. That hydrochloric acid in stomach contents inhibits the production of carbon dioxid is amply borne out by fermentation experiments.

TABLE 3.—Influence of the Presence of Food on Relative Gas Values

Experiment	300 C.c. Room Air Injected	10 Min.		20 Min.		35 Min.		50 Min.		65 Min.		Average		Remarks
		CO_2	O_2	CO_2	O_2	CO_2	O_2	CO_2	O_2	CO_2	O_2	CO_2	O_2	
1	Fasting.....	5.5	19.3	5.8	18.4	6.1	17.9	5.7	17.4	4.6	14.7	5.54	17.54	Stomach secretion with saliva; T.A. 15; HCl 6
	1½ hours after full breakfast	4.1	19.7	6.1	18.1	7.1	16.9	6.8	16.8	3.2	18.1	5.46	17.92	Stomach contents well digested; T.A. 30; HCl 15
2	Fasting.....	2.7	20.0	4.3	19.5	4.4	17.7	5.3	16.5	5.4	18.2	4.42	18.38	Mucus and saliva; no free HCl
	2 hours after full breakfast	1.4	19.2	1.9	16.8	4.0	18.0	4.9	16.5	5.3	16.9	3.50	17.48	Contents, T.A. 20; free HCl 0
3	Fasting.....	4.0	19.9	4.9	18.9	5.6	18.3	6.5	18.6	7.1	16.6	5.62	18.46	Mucus and saliva; T.A. 16; free HCl 5
	1½ hours after full breakfast	5.7	19.2	6.2	16.8	6.7	17.9	6.7	15.7	7.3	16.4	6.52	17.2	Well digested stomach contents; T.A. 37; free HCl 14
4	Fasting.....	3.6	19.6	4.8	18.4	7.6	17.4	6.8	16.9	7.2	17.3	6.0	17.92	1 glass of water 1 hr. before; 50 c.c. stomach contents; T.A. 34; HCl 20
	1 hour after full breakfast	1.7	19.3	8.1	16.9	5.9	17.5	4.1	17.1	4.5	19.0	4.86	17.96	Contents well digested; T.A. 34; free HCl 20

Time designated is number of minutes after introduction of room air into the stomach at which the sample was taken.

Analyses of room air varied: CO_2 from 0.9 to 0.23 per cent. and O_2 from 20 to 20.97 per cent., depending on whether the windows were open or closed, the number of people about, and the number of flames burning in the laboratory.

In order to determine the possibility of fermentation as a source of stomach gas, stomach contents, obtained after the usual Ewald test breakfast from one hundred unselected cases, were incubated at 37 C. for twenty-four hours in saccharimeters. In only thirty-one instances was there any evidence of gas formation as shown either by a large or a few minute bubbles. In seventeen cases only was there a bubble of sufficient size to estimate. In all cases, except three, in which there was any evidence of gas production, there was no free hydrochloric acid present. In the three cases that showed gas in the presence of free hydrochloric acid the total acidity was below 20. All stomach contents without free hydrochloric acid, except four, showed evidence of

fermentation. The presence of free hydrochloric acid in quantity in the stomach contents practically precludes the production of carbon dioxid by fermentation. It is obvious from these experiments, as well as from the absence of marked difference in the carbon dioxid content in air introduced into the fasting and digesting stomach, that fermentation can have little to do with the carbon dioxid content in the stomach gas of normal persons.

COMMENT

These experiments show that within an hour after the injection of room air into a normal stomach, the carbon dioxid reaches a tension equivalent to from 4 to 9 per cent. The carbon dioxid values lie mostly between the pressure at which carbon dioxid is held in arterial blood and alveolar air (5.5 per cent. carbon dioxid), and in the tissues (from 7 to 9 per cent. carbon dioxid).[6] In only one instance in a normal fasting stomach was a carbon dioxid value obtained (10 per cent.) higher than that given for venous blood. A constant reduction of the oxygen content was noted, but the removal of oxygen from the injected air was much less rapid than the passage of carbon dioxide into it. The oxygen content in no instance fell sufficiently to approximate that of alveolar air (14 per cent.) within one hour's time, and in no instance have we found oxygen values as low as those prevailing in arterial blood (from 12 to 13 per cent.). We must conclude, therefore, that when atmospheric air is introduced into the stomach it tends to come into equilibrium as far as its carbon dioxid and oxygen content is concerned with the blood gases of the stomach wall, rapidly in the case of the carbon dioxid, slowly in the case of the oxygen. This corroborates, in part, the experiments of Ylppo,[7] carried out on himself, in which he found that atmospheric air, as such, disappeared from the stomach in from forty to sixty minutes, that the residue had a rather constant oxygen-carbon dioxid ratio, which approximated that of blood gases. Simultaneous alveolar air analyses showed that there was a constant ratio between stomach and blood gases. In our experiments, however, values much higher than those of alveolar air were commonly obtained. Of interest in this connection are the experiments of Haggard and Henderson,[8] who injected air into the abdominal cavity and found that within one hour it came to have a carbon dioxid tension equivalent to that of arterial blood and alveolar air.

It is obvious that gaseous interchange in the stomach is a fundamental physiologic process governed by fixed laws. It is not unlikely

6. Howell, W. H.: A Text Book of Physiology, Philadelphia: W. B. Saunders Company, 1918, p. 689.
7. Ylppo, A.: München. med. Wchnschr. **63**:1650, 1916.
8. Haggard, H. W., and Henderson, Y.: J. Biol. Chem. **38**:71, 1919.

that measurable differences in rates and degrees of diffusion may occur in pathologic processes such as cardiac decompensation (asphyxia), arteriosclerosis, ulcer, carcinoma, dilatation of the stomach, hyperthyroidism, aerophagia, etc., and that the study of the variations in gaseous interchange occurring in the stomach in both general and in gastrointestinal disease may lead to knowledge of clinical value. For example, it has long been assumed that belching is a pastime for the neurotic, an evil habit of which he must be broken by "psychical" measures. It has been spoken of as an "obsessing tic," and a "neuropathic predisposition" postulated. A study of the whole subject of aerophagia in the light of accurate gas analyses may reveal a cause of more compelling therapeutic interest for this unpleasant symptom complex than that which allows it to be viewed in the yellow light of "neurotic perversity." The question of "why do people with stomach trouble belch gas" has never been answered completely.

CONCLUSIONS

1. Atmospheric air introduced into the stomach tends to come into equilibrium with the blood gases within one hour in the case of carbon dioxid, and considerably later, if at all, in the case of oxygen.

2. All the carbon dioxid found in the stomach gas of normal persons, whether fasting or after a full meal, can be accounted for by secretion or diffusion from the gastric mucosa.

3. In the study of stomach gas occurring in pathologic conditions, an upper normal limit of at least 9 per cent. carbon dioxid tension must be postulated.

STUDIES IN THE CHEMOTHERAPY OF BACTERIAL INFECTIONS

II. THE CHEMOTHERAPY OF EXPERIMENTAL LOCALIZED BACTERIAL INFECTIONS WITH SPECIAL REFERENCE TO PLEURITIS *

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In serum and chemotherapeutic investigations in bacterial infections, animals are usually infected by subcutaneous or intraperitoneal injections of the test microorganism resulting in the production of generalized infections associated with bacteremia and terminating fatally in a few days, or in a few weeks, as in experimental tuberculosis. As a general rule, the test animals are very susceptible to the test microparasite, and the results are evaluated by the duration of the lives of treated animals as compared with infected but untreated controls.

In experimental serum therapy of such bacterial infections as are produced by virulent pneumococci, streptococci, meningococci, anthrax bacilli, and so forth, this method is generally satisfactory because owing to the low toxicity of the immune serums for the test animals, relatively large amounts may be given to influence favorably an otherwise rapidly fatal bacteremia and septicemia. But in chemotherapeutic studies in bacterial infections the dosis curativa of a medicament is likely to be but slightly less than the dosis tolerata or the dosis lethalis, and rapidly fatal and generalized infections do not disclose possible, although feeble, curative effects on the part of the compound under study, and thereby fail to yield information of value for the conduct of chemotherapeutic investigations.

For example, the maximum tolerated dose of ethylhydrocuprein hydrochlorid (optochin) for mice, by intravenous and intraperitoneal injection, is approximately from 20 to 40 mg. per kilo of body weight. When these animals are infected with 50 minimum lethal doses of Type I pneumococci, Cohen, Heist and myself [1] found that at least 20 mg. of drug per kilo must be administered at about the same time as the cocci to prolong the lives of approximately 20 per cent. of animals for an indefinite period. This amount was one half or more the highest

* From the Dermatological Research Institute of Philadelphia and the Pathological Laboratories of the Graduate School of Medicine of the University of Pennsylvania.

1. Cohen, S. S.; Kolmer, J. A., and Heist, G. D.: The Protective and Curative Value of Quinin and Urea Hydrochlorid, Ethylhydrocuprein and Other Cinchona Derivatives in Experimental Pneumococcus Infections, J. Infect. Dis. **20**:313, 1917.

tolerated dose and indicates the very small margin between dosis tolerata and dosis curativa of ethylhydrocuprein hydrochlorid for mice with pneumococcus bacteremia. Moore[2] has observed somewhat better results than we in the treatment of pneumococcus bacteremia of mice will the ethylhydrocuprein base, but the margin between the toxic and curative doses was likewise small.

Much better results, however, have been observed by Sands and myself[3] in the treatment of pneumococcus pleuritis of guinea-pigs. We have been able to produce well defined lesions by injecting intrapleurally 0.5 c.c. of twenty-four hour dextrose blood broth cultures of pneumococci of moderate virulence into the right pleural sac; as a general rule, this was followed by the development of acute suppurative pleuritis on both sides with pericarditis. The lesions, however, were not strictly confined to the pleurae since both lungs frequently showed inflammatory changes and pneumococci were generally found in the blood. Extremely virulent cultures were unsatisfactory inasmuch as rapidly fatal bacteremias ensued; cultures of moderate virulence in broth, rather than suspensions in saline solution, produced the best results, the broth probably aiding in the production of suppurative changes.

For guinea-pigs the maximum tolerated dose of ethylhydrocuprein hydrochlorid by intrapleural injection is approximately from 20 to 30 mg. per kilo, being the same or slightly less than the maximum tolerated dose by intravenous injection.[4] The injection of 0.5 c.c. of 1:500 solution into each pleural sac of guinea-pigs weighing 400 gm. within twenty-four hours after the injection of pneumococci, usually cured the pleuritis and prolonged the lives of the animals for indefinite periods.[5] The total amount injected was, therefore, 1 c.c. of 1:500 per 400 gm., corresponding to 10 mg. per kilo and equivalent to one third the maximum tolerated dose. These experiments have indicated that to study the results of treatment of these more or less localized pneumococcus lesions in animals possessing some natural immunity,

2. Moore, H. F.: The Action of Ethylhydrocuprein (Optochin) on Type Strains of Pneumococci in Vitro and in Vivo, and on Some Other Microorganisms in Vitro, J. Exper. M. **22**:269, 1915.

3. Kolmer, J. A., and Sands, J. R.: Chemotherapeutic Studies with Ethylhydrocuprein Hydrochlorid in Experimental Pneumococcus Pleuritis, J. Exper. M. **33**:693, 1921.

4. Kolmer, J. A.: Route of Administration of Drugs in Relation to Toxicity in Chemotherapeutic Investigations, J. Pharmacol. & Exper. Therap. **17**:431, 1921.

5. The protective and curative effects of ethylhydrocuprein hydrochlorid were improved by the addition of sodium oleate and boric acid (Lamar).[6]

6. Lamar, R. V.: Action on the Pneumococcus and Its Experimental Infections of Combined Sodium Oleate and Antipneumococcus Serum, J. Exper. M. **13**:1, 380, 1911; ibid. **14**:256, 1911; ibid. **16**:581, 1912.

they are better for bringing out the curative effects of a drug than is possible in experiments employing highly susceptible animals with rapidly fatal bacteremias.

Experiments in vitro have shown that mixtures of equal parts of pleural pus containing very large numbers of virulent Type I pneumococci and 1:1000 solutions of ethylhydrocuprein hydrochlorid giving a final dilution of 1:2000 result in the complete destruction of all pneumococci in approximately thirty minutes at body temperature. This corresponds to 10 mg. of the drug dissolved in 10 c.c. of pus. If the pus in both pleural sacs of guinea-pigs weighing approximately 400 gm. amounted to 10 c.c., the injection of 2 c.c. of 1:500 solution of drug (1 c.c. into each sac) would give a final dilution of approximately 1:1000. This dose is equivalent to 10 mg. per kilo and even if all the drug were absorbed, it would be at least one third of the maximum tolerated dose.

In other words, it would appear that in experimental pneumococcus pleuritis sufficient ethylhydrocuprein hydrochlorid may be injected into the pleural sacs to render the contents decidedly pneumococcidal without toxic effects, whereas the same amounts injected into the blood are without effect on the local lesions or pneumococcus bacteremia.

Similar results have been observed by Idzumi and myself[7] in the treatment of experimental pneumococcus meningitis of rabbits with ethylhydrocuprein hydrochlorid.

By subthecal injection the maximum tolerated dose is approximately 0.5 c.c. of a 1:500 dilution per kilo of body weight, being equivalent to 1 mg. per kilo. By this route of administration the drug is twenty or more times more toxic than by intravenous injection.

Experiments in vitro with purulent spinal fluids containing virulent Type I pneumococci, have shown that the drug is germicidal in final dilutions of 1:2000 in thirty minutes, 1:4000 in one hour, and 1:10,000 in one and a half hours at body temperature.

The subthecal injection of rabbits with 0.5 c.c. of a 1:1000 dilution per kilo within from four to six hours after the subthecal injection of pneumococci of moderate virulence, results in saving a large percentage of animals against an otherwise fatal suppurative meningitis and bacteremia. This dose corresponds to 0.5 mg. per kilo and is at least one half the maximum tolerated dose by subthecal injection.

Assuming that there are from 2 to 3 c.c. of spinal fluid per kilo of body weight, the final dilution of drug in the subarachnoid space

7. Kolmer, J. A., and Idzumi, G.: Chemotherapeutic Studies with Ethylhydrocuprein and Mercurophen in Experimental Pneumococcus Meningitis in Rabbits, J. Infect. Dis. **26**:355, 1920.

was approximately 1:6000, providing diffusion was complete; according to the results of the bactericidal tests in vitro, this dilution should possess pneumococcidal activity.

The intravenous injection of rabbits with 10 mg. of ethylhydrocuprein per kilo (equivalent to one half the maximum tolerated dose) had no influence on the course of pneumococcus meningitis; in fact, the animals succumbed somewhat more rapidly owing to lowered resistance due to the infection. But, as stated above, the subthecal injection of 0.5 mg. per kilo (equivalent to one half the maximum tolerated dose by this route) was frequently followed by beneficial results.

In my opinion, the treatment of experimentally infected serous cavities and especially the pleural cavities, constitutes a procedure of distinct value in chemotherapeutic studies in bacterial infections when the curative dose of a compound is likely to be but slightly less than the maximum tolerated dose. In serum therapy or in chemotherapy with such arsenical compounds as arsphenamin in spirochetic or trypanosome (*Tr. equiperdum*) infections, when the curative amount is many times less than the toxic amount, generalized infections are suitable, since the compound may be given in relatively large doses without danger of poisoning.

Studies in the production of experimental tuberculous pleuritis by Ogawa and myself,[8] have shown that it is possible to produce a tuberculous infection limited to the pleurae and lungs with such extension of the disease to the pericardium and lymph glands as occurs by direct lymphatic absorption and continuity of tissues. The intrapleural injection of guinea-pigs with bovine tubercle bacilli is followed by metastases to the spleen, liver and other organs, that is, a generalized infection follows. Human tubercle bacilli likewise produce generalized infections but in not as high a percentage of animals. Human tubercle bacilli injected into the pleural cavities of adult rabbits generally (but not always) resulted in localized lesions; bovine bacilli regularly produced generalized lesions in these animals. Bovine and human tubercle bacilli injected into the pleural cavities of adult white rats and adult dogs have resulted in the production of localized lesions. By suspending the bacilli in broth instead of saline solution, the local supprative changes generally have been increased. While extensive chemotherapeutic studies have not been made with these lesions, I believe that localized tuberculous pleuritis and pneumonitis offer more favorable lesions for studies in vivo than generalized and widespread lesions, the medicaments being injected into one or both pleural cavities at varying intervals after the injection of the bacilli into the right sac.

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8. Kolmer, J. A., and Ogawa, I.: Experimental Tuberculous Pleuritis as an Aid to Chemotherapeutic Investigations in Tuberculosis, Am. Rev. Tuberc. **6**:437, 1921.

In this connection the experiments of Gay and Stone [9] in the production of experimental pleuritis in rabbits are of interest. These investigators have studied the effects of vaccine and serum therapy on these lesions, and later Gay and Morrison [10] experimented with various dyes injected into the infected cavities, but with negative results.

For the production of localized bacterial infections of serous cavities for purposes of chemotherapeutic research it would appear necessary to select test animals possessing some natural immunity for the test bacterium; furthermore, the bacterium should be of moderate rather than of extreme virulence. These factors decrease the chances of producing generalized infections and bacteremias and favor the development of localized lesions spreading only by direct continuity of tissues. Under these conditions subtoxic amounts of medicament injected into the cavities may produce therapeutic results even when diluted with inflammatory exudates and thereby yield information of value in chemotherapeutic investigations.

SUMMARY

1. Studies with ethylhydrocuprein hydrochlorid (optochin) in the treatment of experimental pneumococcus pleuritis and meningitis have indicated that in chemotherapeutic investigations in bacterial infections, localized infections of serous cavities offer a more favorable means for eliciting therapeutic effects of a medicament than generalized infections and bacteremias.

2. In localized infections of serous cavities it is possible to inject into the sacs sufficient amounts of medicament to render the contents bactericidal and curative. These amounts may be at least one half the maximum tolerated doses. In rapidly fatal generalized infections with bacteremias, however, the intravenous injection of one half the maximum tolerated dose may be without therapeutic effects.

3. Localized bacterial infections of serous cavities would appear to be especially useful for chemotherapeutic studies with medicaments possessing high toxicity when the margin between dosis tolerata and dosis curativa is small.

4. In the production of localized infections of such serous cavities as the subarachnoid space, pleural sacs and pericardium, test animals possessing some natural immunity to the test bacterium should be

9. Gay, F. P., and Stone, R. L.: Experimental Streptococcus Empyema. Attempts at Prevention and Therapy by Means of Vaccines and Serum, J. Infect. Dis. **26**:265, 1920.

10. Gay, F. P., and Morrison, L. F.: Experimental Streptococcus Empyema. Attempts at Dye Therapy, J. Infect. Dis. **28**:1, 1921.

chosen, like the guinea-pig for pneumococcus pleuritis and pericarditis, the cat or dog for pneumococcus meningitis and the dog or rat for tuberculous pleuritis. The test microorganism should be of moderate rather than extreme virulence, in order to reduce the invasiveness or aggressiveness of the bacteria for the blood and other organs.

AN EXPERIMENTAL AND CLINICAL STUDY OF QUINIDIN SULPHATE: I. EXPERIMENTAL*

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Experiments were devised for the purpose of studying some of the effects of quinidin on the normal dog and guinea-pig heart. The method employed was comparatively simple. Dogs were fully anesthetized with ether, except in one instance when anesthesia was secured by means of chlorbutanol and morphin. The right fore leg and left hind leg were shaved, and suitable electrodes applied and connected to the string galvanometer in the usual way. All experimental electrocardiograms were therefore derived from Lead II. The thorax was not opened in any case; no direct auricular contacts were employed, and all observations were conducted on the spontaneously beating heart. When observations on the vagi were desired, these nerves were isolated for a considerable distance in the neck, sectioned, and the peripheral end stimulated from the secondary coil of the ordinary inductorium. A signal in circuit with the primary coil marked the beginning and end of stimulation. Quinidin sulphate supplied by Merck, the same preparation which was used in the wards, was dissolved in physiologic solution of sodium chlorid and injected in measured amounts from a buret into the femoral vein. Atropin, which was used in one animal, was injected subcutaneously.

Anesthesia was secured in guinea-pigs by means of ether in conjunction with urethane or paraldehyd. The electrocardiogram was recorded from an axial lead, comparable to the conventional Lead II, derived in some instances from metal electrodes, one inserted beneath the skin of the neck, the other thrust into the rectum. Where polarization became appreciable, the metal contacts were supplanted by nonpolarizable boot electrodes inserted beneath the skin of the neck and left hind leg. Quinidin sulphate, dissolved in distilled water by the addition of a few drops of concentrated sulphuric acid, was given to these animals by stomach tube in one massive dose of 0.67 gm. No observations on the vagi were attempted. In all other respects the procedure was the same as for the dogs.

In each animal a complete series of control records was made. When vagus effects were to be studied, the tonic activity of both nerves was established, and the minimal effective stimulus determined. An accurate time record of all electrocardiograms and experimental pro-

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cedures was kept. In dogs the immediate effect of each intravenous injection was thoroughly studied in records which began with the injection and were continued at frequent intervals, and the remote effects of the total dosage were observed throughout each experiment until the animal died from quinidin poisoning. In guinea-pigs the steadily progressing changes in the electrocardiogram were photographed at frequent intervals over a period of sixty to ninety minutes, at the end of which time death usually occurred.

Instead of reproducing detailed protocols of the experiments, I shall summarize the more important facts which have been established in analysis and measurement of approximately 1,000 feet of records.

Rate of Impulse Discharge from the Pacemaker.—The inevitable result in all experiments is ultimate retardation of the rate of beating, but temporary increases are frequently seen immediately after single injections of the drug. Lewis and his associates [1] have shown that retardation is due to a direct action on the Purkinje structures of the pacemaker, for it is independent of the action of atropin. This may also be inferred from our experiments, for it occurs in spite of the contrary effect which is to be expected from paresis of the vagi by quinidin. Temporary increase in rate of beating after single injections is to be explained either as the result of a predominant effect on the vagi, or delay of the effect on the structures of the pacemaker. The latter seems much the more probable. Quinidin retards the rate at which impulses are discharged from the pacemaker whether the latter be situated in the *S-A* node or the *A-V* node, a fact well illustrated in the case of Dog 1. Immediately after the first injection of the drug, and coincidentally with the development of a high grade of intra-auricular block, the function of pacemaker was assumed by the *A-V* node, but the rate of beating was progressively slowed notwithstanding. These results are in accord with those obtained by Schott,[2] Boden and Neukirch [3] and Lewis, et al.[1] Cohn and Levy [4] saw no constant effect on rate of beating in their dogs.

Intra-Auricular Conduction.—Lewis and his associates have shown that quinidin greatly slows conduction in the auricle when the heart is driven at a constant rate of about 200 per minute. This disturbance in conduction proceeds to "intra-auricular block," which is characterized by gross irregularity of the auricular curves. This phenomenon of intra-auricular block appears in electrocardiograms of hearts beating in response to their own rhythm in the earlier paper of Boden and Neukirch, but was evidently misinterpreted by these authors. So far

1. Lewis, Drury, Iliescu and Wedd: Heart **9**:55, 1921.
2. Schott: Deutsch. Arch. f. klin. Med. **134**:208, 1920.
3. Boden and Neukirch: Deutsch. Arch. f. klin. Med. **136**:181, 1921.
4. Cohn and Levy: Proc. Soc. Exper. Biol. & Med. **18**:283, 1921.

as I am aware, it has not been described in the spontaneously beating heart. It is evident that intra-auricular block which is responsible for irregularity of the auricular curves when the heart is driven at a constant rate will be represented in the heart which beats in response to its own impulses by regular, but arrhythmic, auricular waves. I have noted this occurrence in a patient shortly after the resumption of normal mechanism, and have frequently produced the condition in experiment. In the spontaneously beating heart intra-auricular block is essentially a condition in which the auricles and ventricles beat independently of each other, at nearly the same rates, or at widely different rates. The auricle responds to the *S-A* node, the ventricle to the *A-V* node. In the early stage of development the auricular rate slows, but remains rhythmic; later, the auricular systoles become grossly arrhythmic. Assumption by the *A-V* node of the function of pacemaker for the ventricle is probably due both to actual starvation of its natural quota of transmitted impulses, and to irregularity of the auricular intersystolic intervals. The fact that the *A-V* node always assumes this function, at least in the earlier stages of poisoning, is proof that it is not functionally depressed to the same extent as the auricular muscle, although, as has been noted above, its rate of discharge of impulses is progressively retarded as poisoning increases. One might justly infer that if for any reason the *A-V* node were unable to assume pacemaker function following intra-auricular block, the resulting condition would closely approximate what is commonly known as "sino-auricular block." In other words, it is suggested that so-called "sino-auricular block" may really be intra-auricular block unaccompanied by *A-V* nodal escape. One would then expect *S-A* block to consort with intra-auricular block at a comparatively late stage of poisoning, which is precisely what occurs (Figs. 5 and 15). Bearing in mind the established relation of the vagus to *S-A* block, it is significant that the block occurs after a large part of the paretic action of quinidin on the vagus has been exerted. As Lewis and his associates [5] have suggested, and as one may infer from the paper of Boden and Neukirch, intra-auricular block is usually partial, but may be complete, resulting in auricular asystole (Fig. 10).

Electrocardiograms of intra-auricular block are likely to be confused with those of *A-V* rhythm, but a careful analysis of the curves clearly defines the condition in a manner presently to be explained. It is at this point that Boden and Neukirch were mislead. The hypothesis of *A-V* rhythm is inconsistent with our conception of intra-auricular block, for in the former it is clear that the whole heart is responding to impulses from but one center, whereas in the latter, two separate

5. Lewis, Drury and Iliescu: Heart **9**:21, 1921.

centers control auricles and ventricles. It is, therefore, impossible to conceive that the two entities might coexist. Development of the conception of intra-auricular block improves our sense of criticism in regard to certain cases which might otherwise be interpreted unreservedly as *A-V* rhythm. For example, two electrocardiograms recently published by Richardson [6] (Figs. 3 and 4 of his paper) present certain features which are not in agreement with pure *A-V* rhythm as it is commonly understood. Richardson's criteria for *A-V* rhythm include inversion of *P*, and to explain the upright *P* of his Figure 3, he suggests interference between the *S-A* and *A-V* nodes, both active. To carry this a step further, may not his Figure 3 represent partial intra-auricular block with continuous escape of the *A-V* node? One should note the striking resemblance of this record to Figure 9 of the present paper. Similarly, the arrhythmicity and protean contour of the *P* waves of his Figure 4 may well be due to intra-auricular block, accompanied, in this instance, by arrhythmic escape of the *A-V* node. Digitalis may have induced intra-auricular block in this patient. It is significant that the condition has been produced experimentally in dogs [5] by means of strophanthin.

Lewis has shown that in hearts driven at a constant rate the irregularity of the auricular waves from intra-auricular block is abolished by vagus excitation. In my experiments with the normally beating heart vagus stimulation promptly abolished intra-auricular block, for which sequential chamber contraction in response to one center, the *S-A* node, was substituted. The right vagus was employed exclusively in these experiments (Figs. 18, 19, 20, 21, 22, 23).

Figures 1 to 11, inclusive, recorded from Dog 1, portray a remarkable series of events due to intra-auricular block. Figure 2 could not of itself be distinguished from *A-V* rhythm. It represents the stage when the auricular rate has slowed, but is still rhythmic. The *P* waves are buried in the *Q R S* group. Consideration of Figure 3, however, definitely sets aside the question of *A-V* rhythm. The auricle is now grossly arrhythmic, the interauricular intervals varying from 0.536 to 0.64 second. On the other hand, the interventricular intervals, exclusive of accidental beats, are equal. *R* bears no sequential relation to *P*. The latter is entirely independent of *R*, and whether it precedes, follows, or is submerged in *R* is purely a matter of accident. The only exception to this is seen when the impulse from the *S-A* node, by reason of its arrhythmicity, chances to arrive in the ventricle when the latter is not refractory. The ventricle then responds in the usual sequential fashion, disturbing temporarily the rhythmic *A-V* nodal control of the ventricle. Two examples of this appear in Figure 3. When *P* falls

6. Richardson: Arch. Int. Med. **29**:253 (Feb.) 1922.

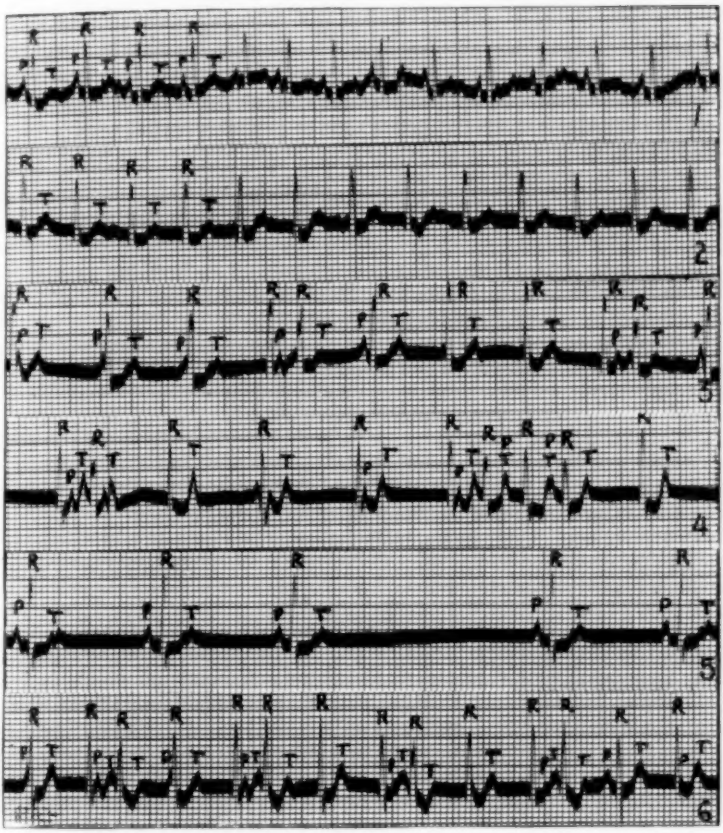

Fig. 1 (D-I-02).—Rate, 160; *P-R*, 0.068; *Q R S*, 0.038. Unless otherwise stated, one scale division of abscissae equals 0.04 second, of ordinates, 10^{-4} volt, in this and all succeeding figures. Time measurements made with magnification of 18 diameters, accurate within a few thousandths of a second. All experimental electrocardiograms from Lead II. For full description see text.

Fig. 2 (D-I-10).—Rate, 160; *Q R S*, 0.056.

Fig. 3 (D-I-11).—Ventricular rate, exclusive of extra beats, 116; auricular rate circa 105; *Q R S*, 0.044; *P-R* of extra beats varies from 0.116 to 0.128.

Fig. 4 (D-I-12 B).—Ventricular rate, exclusive of extra beats, 97; auricular rate circa 89; *Q R S*, 0.054; *P-R* of extra beats varies from 0.104 to 0.168.

Fig. 5 (D-I-13).—Rate, 69; *P-R*, 0.096; *Q R S*, 0.048. Long pause exactly double the shorter diastole.

Fig. 6 (D-I-14 A).—Ventricular rate, exclusive of extra beats, 148; auricular rate circa 127; *Q R S*, 0.054; *P-R* of extra beats, 0.126.

far enough after *R* an extra beat of the ventricle follows. The occurrence of these extra beats of the ventricle affords absolute proof that the tardy *P* is not the representative of backward propagation over the auricle of the *A-V* nodal impulse. It is important to note that the contour of *P* does not differ essentially from the control, Figure 1. Figure 4 portrays a more advanced degree of the same condition. The

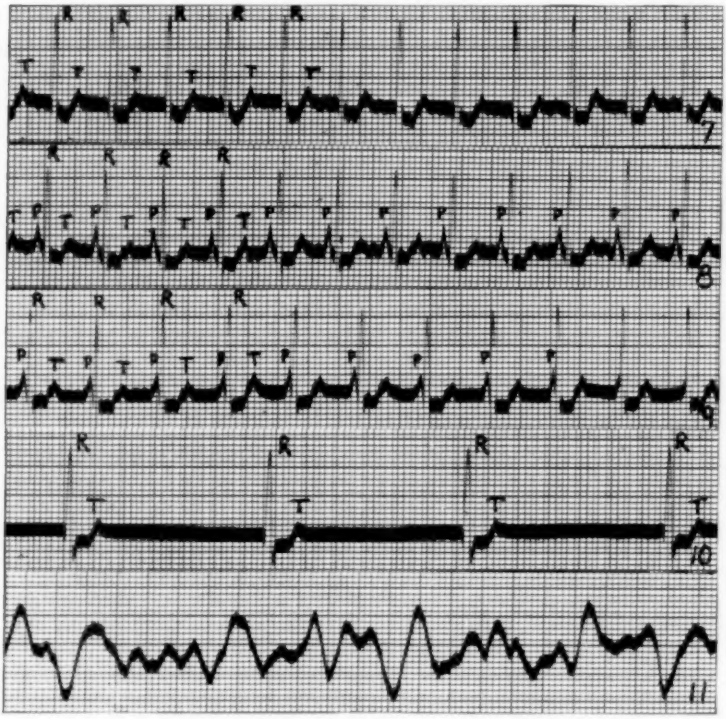

Fig. 7 (D-I-17).—Rate, 158; *Q R S*, 0.056.

Fig. 8 (D-I-18).—Rate, 158; *Q R S*, 0.056.

Fig. 9 (D-I-19).—Rate, 136.

Fig. 10 (D-I-20 A).—Rate, 45; *Q R S*, 0.088. Not all time lines accurate.

Fig. 11 (D-I-27).—Ventricular fibrillation.

auricle is now so arrhythmic that three extra beats of the ventricle in response to sino-auricular impulses occur in sequence.

Figure 5 shows sino-auricular block occurring at a later stage of poisoning. Discharge of impulses from the *A-V* node is inhibited, the ventricle responds only to the *S-A* node, and the auricle has become

rhythmic. Figures 6, 7 and 8 show gradual recovery from intra-auricular block. In Figure 6 one sees a return of auricular arrhythmia, control of the ventricle by the *A-V* node at a rate of 148 per minute, and many extra beats of the ventricle as described in Figure 4. In Figure 7 the auricular arrhythmia has disappeared, but the auricle is slower than the ventricle, and the *S-A* node and *A-V* node still control auricle and ventricle, respectively. *P* is buried in *R*. Figure 8 shows the rates of auricle and ventricle nearly equal, *P* having emerged from *R*. The *P-R* interval is shorter than that of the control, however, and

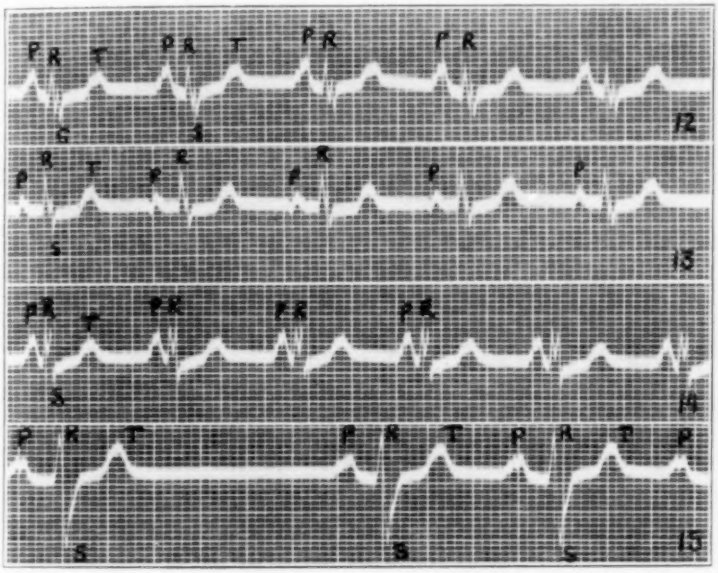

Fig. 12 (D-III-53-1).—*P-R*, 0.1; *Q R S*, 0.068.

Fig. 13 (D-III-54-1).—*P-R*, 0.112; *Q R S*, 0.068.

Fig. 14 (D-III-55-1).—*P-R* of 0.06 does not represent transmission time.

Fig. 15 (D-III-61-5).—Rate, 83; *Q R S*, 0.112; usual *P-R* 0.152, after long pause *P-R* 0.128.

the chambers still beat independently. Recovery from intra-auricular block is nearly complete in this record.

Figure 9 shows the auricle once more slowing from renewed intra-auricular block subsequent to a fresh injection of quinidin. Figure 10, recorded ninety seconds after Figure 9, shows complete intra-auricular block, auricular asystole, with ventricular autonomy at 45 per minute. Eventual termination of quinidin poisoning in ventricular fibrillation is revealed in Figure 11. Careful consideration of all the details dis-

played in this series of records emphasizes the point that, although as a rule all changes in function brought about in the various individual structures by quinidin poisoning proceed uniformly, at certain times single effects and different groups of effects predominate to the relative exclusion of others.

A less striking occurrence of intra-auricular block, progressing only to the point of slight slowing of the auricular rate, was noted at one time in Dog 3. Figure 12 shows the character of the electrocardiogram at a rather late stage of poisoning. Five minutes later a considerable change in the character of *P* was seen, as shown in Figure 13. Figure

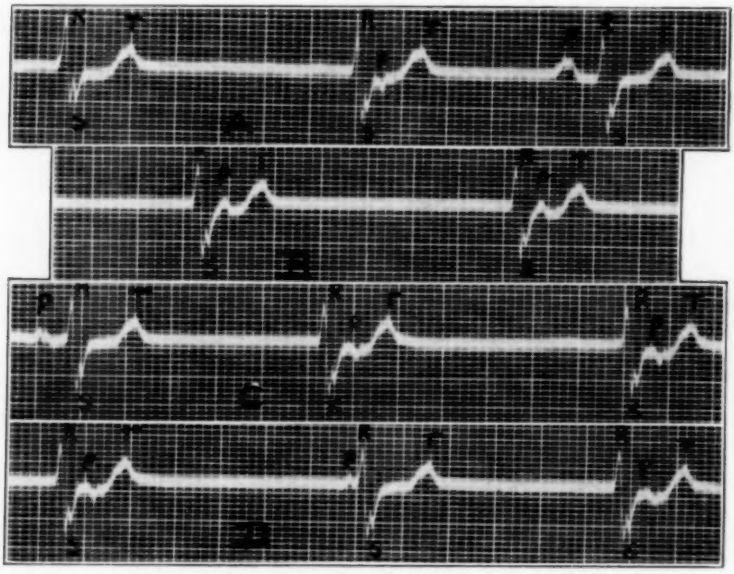

Fig. 16 A (D-III-62).—Rate, 45; *Q R S*, 0.1.
Fig. 16 B
Fig. 16 C
Fig. 16 D

14 follows six minutes after Figure 13, and portrays slight slowing of the auricular rate. Figure 15 shows sino-auricular block at a still later stage of poisoning, and Figure 16 (A, B, C and D) depicts intra-auricular block in conjunction with a very slow *A-V* nodal rate of discharge. The last cycle in *A* and the first in *C* are examples of extra beats of the ventricle, comparable to those already described in connection with Dog 1.

Intra-auricular block appearing in a patient (Case 14) shortly after the resumption of normal mechanism is portrayed in Figure 17. The auricle is slowing, while the ventricle continues to respond at regular intervals to the *A-V* node.

The effect of vagus excitation on intra-auricular block is well shown in Figures 18 to 23, inclusive. In all instances the *A-V* nodal rate is inhibited to a greater or less degree with the beginning of stimulation. In all except Figure 19 the intra-auricular block is increased at the onset of stimulation, as shown by greater arrhythmia of the auricular beats. This is promptly succeeded, within a few cycles, by total abolition of the intra-auricular block and resumption of normal sequential chamber contraction by the whole heart. In Figure 19 the block is immediately decreased. Figure 21 is reproduced to show the rapid

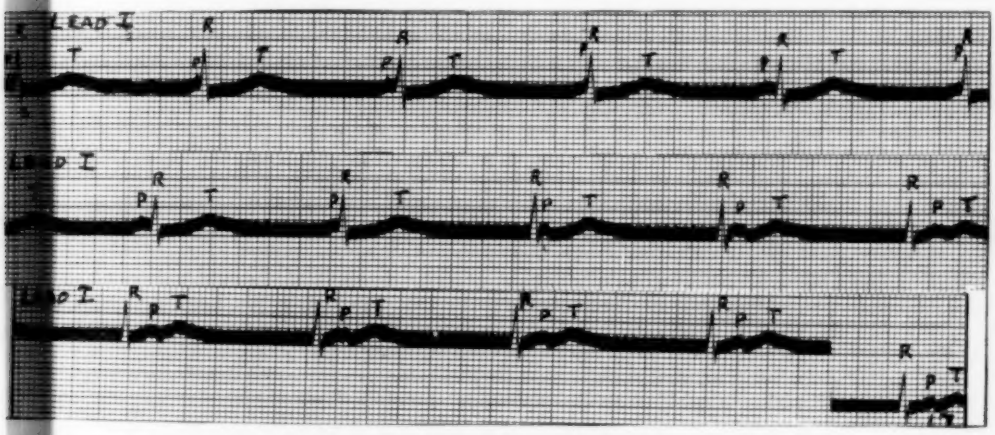

Fig. 17.—Intra-auricular block in a patient (Case 14).

return of intra-auricular block five seconds after cessation of stimulation.

The fact that intra-auricular block could not be produced in guinea pigs is unexplained. *A-V* heart block and intraventricular block are the chief results of quinidin poisoning in these animals.

Auriculo-Ventricular Conduction.—Most investigators have found that quinidin depresses *A-V* conduction in dogs, with which my results are in agreement. It is important to note that, in the naturally beating dog heart, this effect proceeds in direct proportion to the other changes simultaneously occurring in sino-auricular rate, intra-auricular conduction, and intraventricular conduction. It is never individually conspicuous, never advances farther than simple prolongation of the *P-R* interval. No dropped beat of the ventricle due to *A-V* block

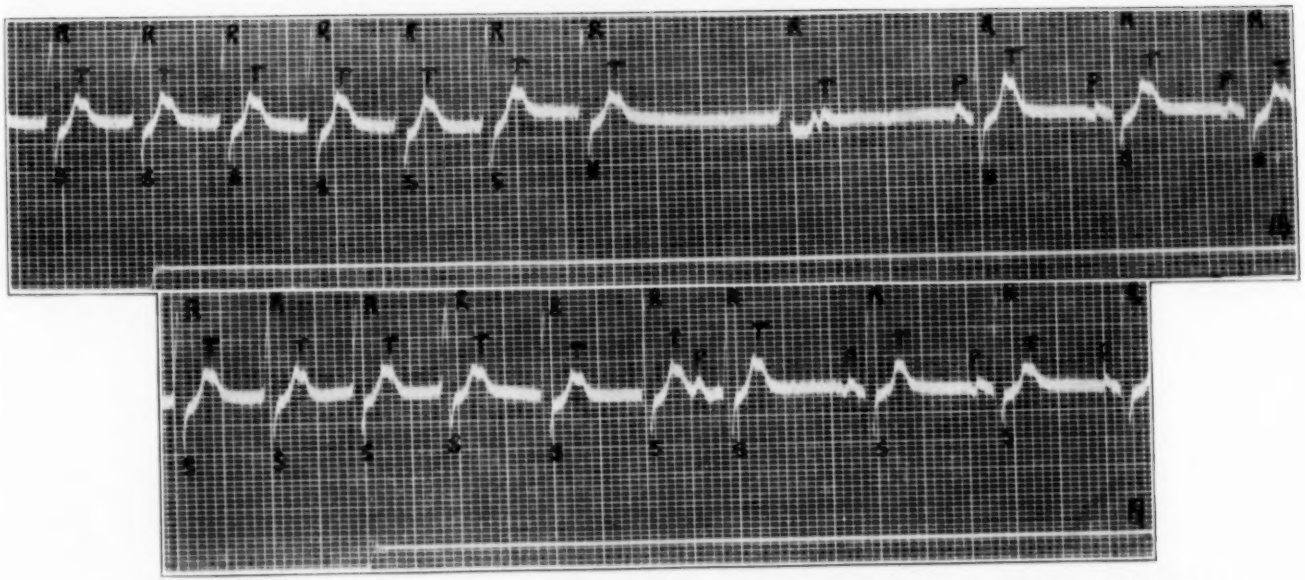

Fig. 18 (D-V-12-1).—Intra-auricular block and vagus stimulation. Signal marks beginning of stimulation. Coil at 9 cm.
Fig. 19 (D-V-11).—As Figure 18. Coil at 9 cm.

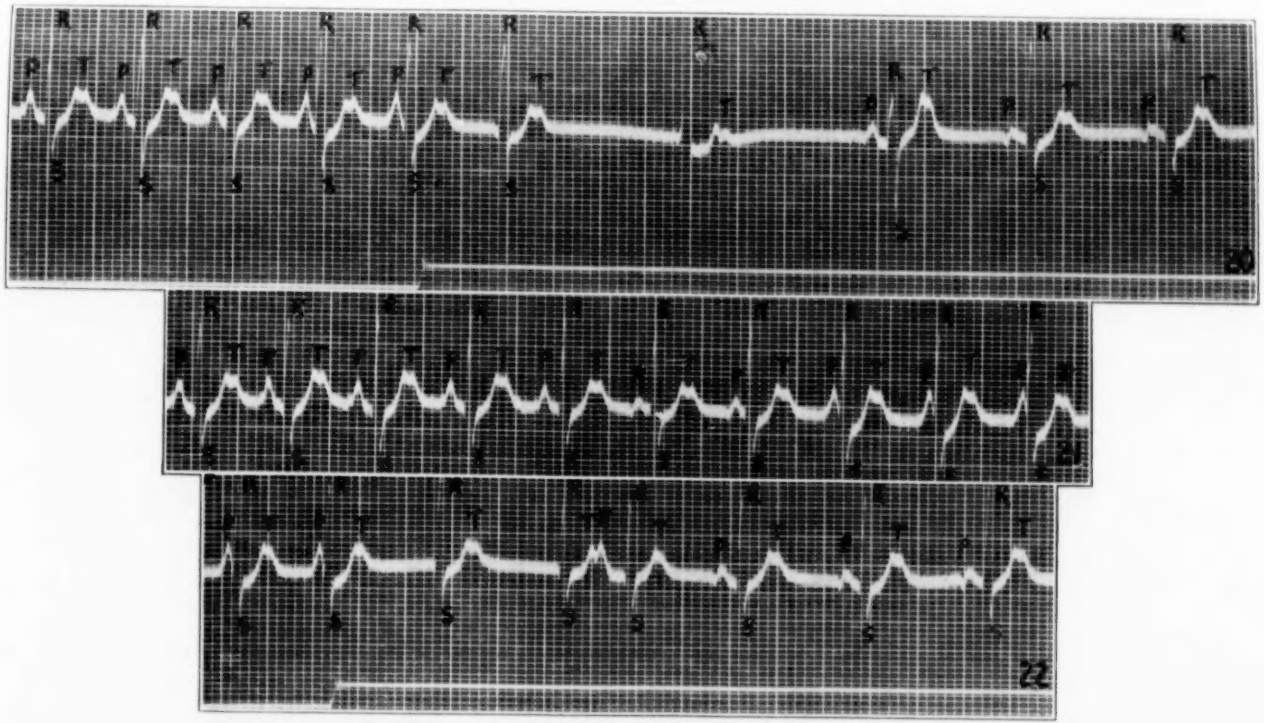

Fig. 20 (D-V-11).—As Figure 18. Coil at 9 cm.

Fig. 21 (D-V-11).—Block returning, five seconds after cessation of stimulation.

Fig. 22 (D-V-14).—As Figure 18. Coil at 9 cm.

occurred in my dogs, even in the very late stages of poisoning when complete branch block was well established.

In the earlier stages of quinidin poisoning in guinea-pigs depression of *A-V* conduction progresses equally with other changes. As poisoning increases, however, a disproportionate effect on *A-V* conduction appears, which in my experiments reached, but never exceeded, the grade of 2:1 heart block. Schott [2] reports much higher grades of partial heart block in his pigs, a statement which has led many clinicians to avoid using quinidin and digitalis together. In only two cases, both reported by Hewlett and Sweeney,[7] has complete *A-V* heart block been regarded as the result of combined action of the two drugs, and in neither is it clear that digitalis alone might not have been responsible.

In my first few experiments with guinea-pigs, in which Schott's technic was closely followed, high grades of partial *A-V* heart block occurred rather early in the poisoning, progressing in one instance to complete *A-V* dissociation. It was immediately discovered, however, that the onset of block coincided closely with complete cessation of respiration, an event which always takes place very early in quinidin poisoning in the guinea-pig. In all subsequent experiments the factor of asphyxia was ruled out by supplying artificial respiration, with the result that *A-V* block completely disappeared from the early part of the experiment. Changes in *A-V* conduction were proportional to other changes throughout the experiment until a short time before death of the animal, when 2:1 response of the ventricle finally appeared in conjunction with bundle branch block. In each of these latter animals it was shown, prior to the administration of quinidin, that all grades of *A-V* heart block, including complete dissociation, could be produced by asphyxia alone. The precaution of ruling out asphyxia was not taken by Schott. From these results it is clear that the greater part of the *A-V* heart block reported by Schott was due to asphyxia, not to quinidin. It is true, however, that in the guinea-pig quinidin does produce an effect on *A-V* conduction out of proportion to changes in intra-auricular conduction in so far as the two are demonstrable when the heart is permitted to beat naturally, but the effect appears too late in the course of poisoning to be clinically applicable. So far as we have been able to determine by clinical and experimental means there is no direct contraindication to the use of quinidin and digitalis in combination. We have been in the habit of withholding quinidin until the full effect of digitalis has been secured simply because we believe digitalis to be the most essential weapon with which to combat cardiac decompensation, and because our best opportunity of studying the rôle

7. Hewlett and Sweeney: J. A. M. A. **77**:1793 (Dec. 3) 1921.

of auricular fibrillation in cardiac failure is offered when all other factors contributing to that failure have been as far as possible removed.

Figures 24 and 25 show the highest grade of *A-V* heart block obtained in guinea-pigs. The records are from different animals, registered 64 and 75 minutes, respectively, after the single dose of 0.67 gm. quinidin. Artificial respiration was being maintained at the rate of 25 per minute. In addition to *A-V* block, both records show considerable delay in conduction through the right branch of the bundle.

Intraventricular Conduction.—Disturbance of intraventricular conduction manifests itself initially in dogs and guinea-pigs by an increase in the *Q R S* interval which is generally comparable to changes in

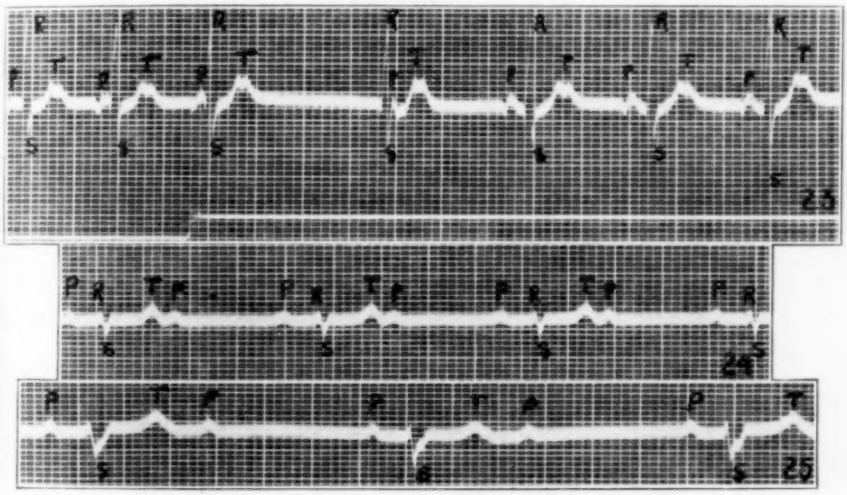

Fig. 23 (D-V-15).—As Figure 18. Coil at 9 cm.

Fig. 24 (P-V-31-1).—2:1 response of the ventricle.

Fig. 25 (P-VII-20-2).—As Figure 24. (In this record ordinates do not exactly equal 10^{-4} volt; resistance exceeds 2,000 ohms, and string overshoots slightly.)

intra-auricular and *A-V* conduction. With deeper poisoning, delay in conduction through one or both branches begins to appear. As I have stated in a previous paper,[8] this delay in branch conduction is to be explained on the basis of differential widening of the refractory periods of the two main divisions of the bundle. Rapid development of the dextrocardiogram or levocardiogram, or alteration of the dextrocardio-

8. Korns: Arch. Int. Med. **30**:158 (Aug.) 1922.

gram and levocardiogram, follows single and repeated injections of quinidin, with eventuation in complete bundle branch block.

Figures 26 to 30, inclusive, portray the development of right bundle branch block in Dog 5. The control (Fig. 26) shows that the dextro-

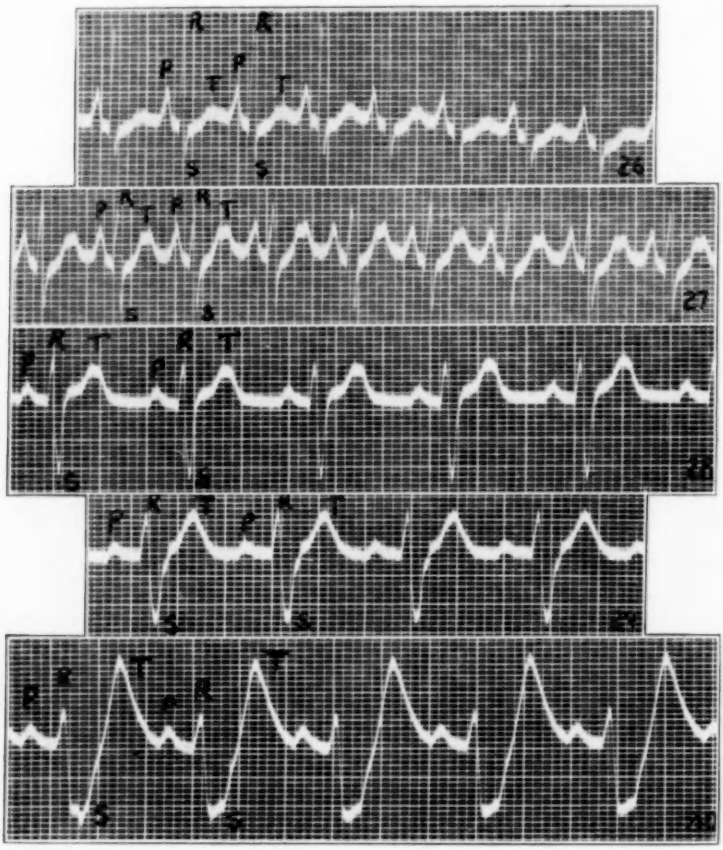

Fig. 26 (D-V-02).—Rate, 192; *P-R*, 0.072; *Q R S*, 0.042.
Fig. 27 (D-V-10).—Rate, 172; *P-R*, 0.08; *Q R S*, 0.042.
Fig. 28 (D-V-21-1).—Rate, 107; *P-R*, 0.112; *Q R S*, 0.08.
Fig. 29 (D-V-22-4).—Rate, 107; *P-R*, 0.15; *Q R S*, 0.12.
Fig. 30 (D-V-22-5).—Complete right bundle branch block.

cardiogram is normally predominant. Figure 27 shows the rapid advancement of the levocardiogram (lengthened refractory period of the right branch) immediately following the initial injection of 0.1 gm. quinidin. Figures 28, 29 and 30 display further gradations in the

process with increasing dosage. A similar series of steps in the development of left bundle branch block (Dog 2) are presented in Figures 31 to 35, inclusive.

Differential widening of the refractory periods of both the right and left branches of the bundle is depicted in a series of records from Pig 5 (Figs. 36 to 44, inclusive). The disturbance of conduction develops first, and remains of higher grade throughout, in the left

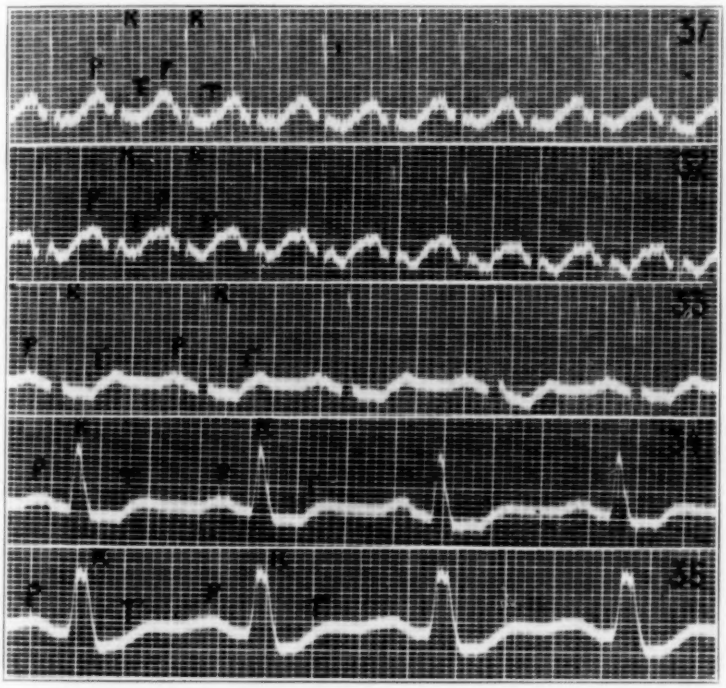

Fig. 31 (D-II-02).—Rate, 202; *P-R*, 0.084; *Q R S*, 0.04.
Fig. 32 (D-II-12-2).—Rate, 194; *P-R*, 0.084; *Q R S*, 0.04.
Fig. 33 (D-II-44-1).—Rate, 97; *P-R*, 0.12; *Q R S*, 0.048.
Fig. 34 (D-II-51-3).—Rate, 81; *P-R*, 0.16; *Q R S*, 0.084.
Fig. 35 (D-II-54-5).—Complete left bundle branch block.

branch. It is of interest to note, in Figure 40, that the long refractory period of the left branch is compensated when a ventricular beat is dropped, for the ensuing complex shows nearly synchronous fusing of the dextrocardiogram and levocardiogram. Deficient branch conduction appears because the refractory period of the branch is longer than that of the *A-V* node. In Figure 41 the refractory period of the branch

has become too long to be compensated for by one dropped beat of the ventricle.

Left bundle branch block appearing in a patient (Case 27) after a total of 6 gm. quinidin is displayed in Figure 45. It disappeared shortly after withdrawal of the drug (Fig. 46). One similar case has been recorded in the literature, that of White, Marvin and Burwell.[9]

Changes in the T Wave.—Many variations of the end deflection *T* have been ascribed to quinidin. In analyzing my experimental curves

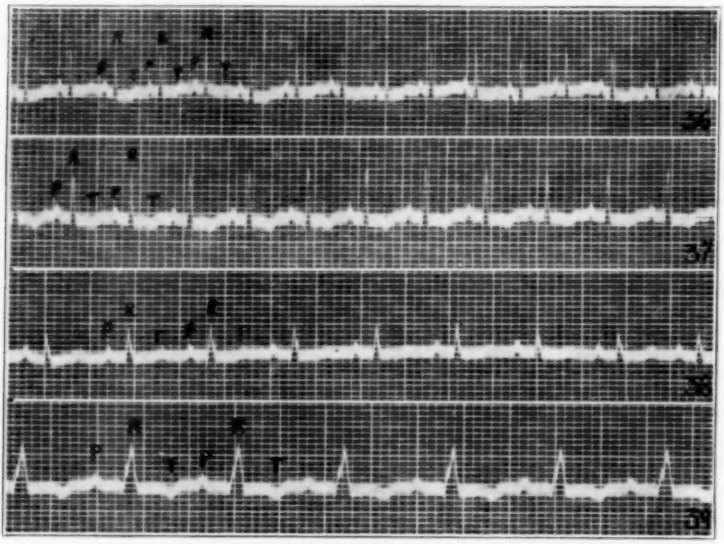

Fig. 36 (P-V-02).—Rate, 272; *P-R*, 0.052; *Q R S*, 0.016.
Fig. 37 (P-V-16-1).—Rate, 220; *P-R*, 0.076; *Q R S*, 0.028.
Fig. 38 (P-V-19-3).—Rate, 164; *P-R*, 0.088; *Q R S*, 0.036.
Fig. 39 (P-V-24-1).—Rate, 127; *P-R*, 0.156; *Q R S*, 0.072.

I have been struck by the fact that in every case the voltage of *T* has altered early in the experiment, and furthermore, its voltage has always initially increased in the direction which will conform with the branch lesion to be found in the late stages of poisoning. Comparing Figure 27, from a dog which eventually developed right bundle branch block, with Figure 32, from a dog which developed left bundle branch block, it is found that, whereas in the former the effect of the first injection of quinidin was to increase the voltage of *T* by 300 microvolts

9. White, Marvin, and Burwell: Boston M. & S. J. **185**:647 (Dec. 1) 1921.

(3×10^{-4}), in the latter the first effect was a deepening at T. A similar effect was observed in Pig 5. It will be recalled that this animal showed greater prolongation of the refractory period of the left than of the right branch, although that of both branches was widened. Reference to Figure 37 shows that an originally upright T was inverted by the first quinidin injection. It later became isoelectric, then upright,

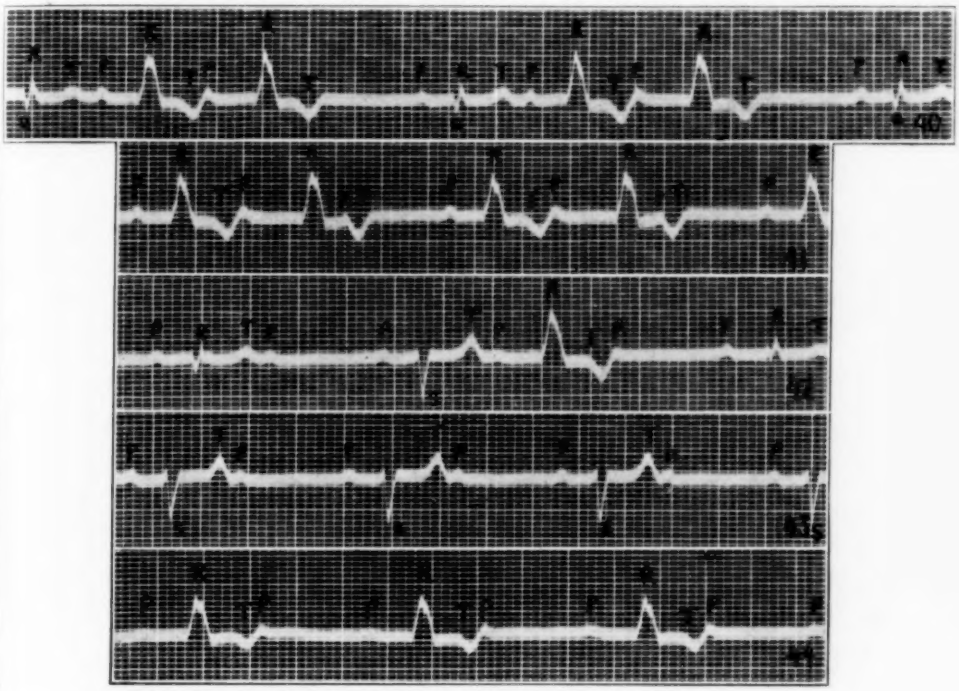

Fig. 40 (P-V-27-1).—Long refractory period of the left branch is compensated when ventricular beat is dropped.

Fig. 41 (P-V-28-1).—Complete left bundle branch block; partial A-V block.

Fig. 42 (P-V-30-2).—Differential widening of refractory periods of right and left branches.

Fig. 43 (P-V-32-2).—Recovery of left branch, involvement of right branch.

Fig. 44 (P-V-33-2).—Eventuation in 2:1 A-V block and complete left bundle branch block.

and again inverted, apparently fluctuating with the refractory period differences of the branches.

The exact nature of the T wave has never been fully elucidated. Wilson and Herrmann [10] believe that the exaggerated T wave which

10. Wilson and Herrmann: Arch. Int. Med. **26**:153 (Aug.) 1920.

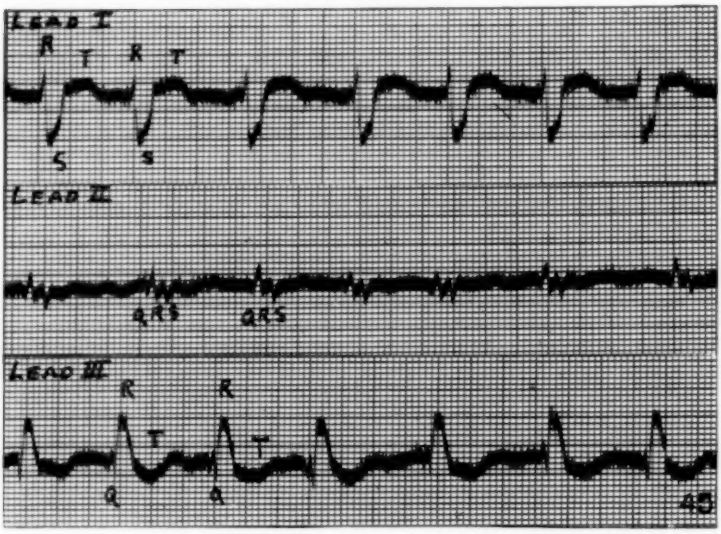

Fig. 45.—Left bundle branch block in a patient (Case 27).

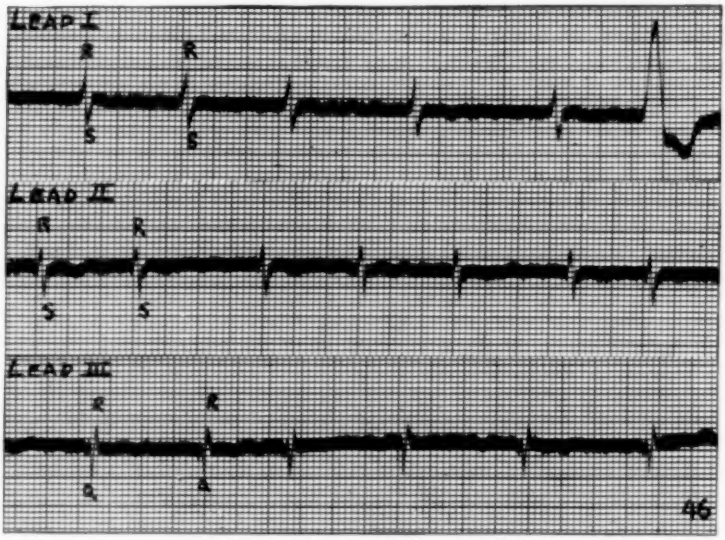

Fig. 46.—Recovery of conduction in left branch in Case 27 after withdrawal of quinidin.

appears in Lead II of the dog's electrocardiogram after division of the right branch of the *A-V* bundle is due to early deactivation of the left ventricle in comparison with the right ventricle, and vice versa. The observations above described suggest that changes in the character of *T* under quinidin are the first delicate indications of earlier deactivation of one or the other ventricle, hence the initial indications of lengthening of the refractory period of the right or left branch of the *A-V* bundle.

Action on the Vagi.—The careful observations of Lewis and his co-workers [1] demonstrate conclusively that quinidin, in doses comparable to those used clinically, exerts a striking paretic effect (peripheral) on the vagi. My own observations were incidental to the examination of other effects. They were made on hearts controlling their own rate of beating, and the results are therefore complicated by slowing due directly to quinidin, and by other factors. Nevertheless, a definite qualitative paretic effect was demonstrable. In one animal the minimal effective stimulus was noted with the secondary coil at a distance of 8 cm. from the primary. Twenty minutes after the first injection of 0.1 gm. the coil was moved to 4 cm. for the minimal effective stimulus. Three minutes after the second injection of 0.1 gm., before time for recovery had been allowed, 0.5 cm. was the coil distance for minimal vagus effect. No response whatever could be obtained after the third injection of 0.1 gm. A result similar to this was noted in one other animal. The so-called "paradoxical action" described by Lewis was not encountered.

Cause of Death from Quinidin.—All my dogs died of ventricular fibrillation, respiration stopping only a few minutes before death. As other workers have observed, the greater the fractionation of dosage, the further is fatal poisoning postponed. Guinea-pigs, if let alone, die an early death from aphyxia due to rapid failure of automatic breathing. If artificial respiration be supplied, however, these animals resist the poison vigorously. In order to observe the late effects of poisoning in one of the pigs it was necessary to administer a second dose of 0.67 gm. Death occurs in these animals, never by ventricular fibrillation, but through gradual slowing and final inhibition of the whole heart.

Aside from fatal terminations due to emboli, which will be discussed in a subsequent paper, it is probably too early to make the statement that quinidin has been directly responsible for the death of any patient. There are many factors to be accounted for in sudden cardiac death. If the drug shall be held solely responsible for sudden fatality, the event must be occasioned by some disastrous effect on the cardiac mechanism. Two suggestions appear in Lewis' paper: (1) the possibility, under quinidin, of long standstill of the ventricle consequent upon a slight rise in auricular rate, and (2) slowing, or actual standstill, of

the ventricle at the moment of resumption of normal sino-auricular rhythm. The question may not find an answer until continuous electrocardiograms are recorded just before and during death supposedly due to quinidin.

Brief reference may be made to the recent paper of Jackson, Friedlander and Lawrence,[11] concerning the pharmacology of quinidin. For some reason, these authors have disregarded the experimental work of Lewis and his associates, with which a great many of their results are not in agreement. After careful comparison of the methods adopted by the two groups of investigators in reaching their conclusions, one is strongly inclined to believe that none of the positions taken by Lewis has been essentially modified.

SUMMARY AND CONCLUSIONS

Quinidin sulphate exerts the following actions on the normally beating heart of the dog and guinea-pig:

1. It may temporarily accelerate, but ultimately retards, the rate of impulse discharge from the pacemaker, regardless of whether the latter be situated in the *S-A* node or the *A-V* node. This is probably a direct effect on the Purkinje structures.

2. It produces, in the dog, depression of intra-auricular conduction, leading to partial or complete intra-auricular block. This is described for the first time in the heart beating spontaneously. A relationship between intra-auricular block and so-called "sino-auricular block" is suggested. Criteria are presented which serve to distinguish intra-auricular block from *A-V* rhythm. It is demonstrated that vagus stimulation abolishes intra-auricular block.

It produces, in the guinea-pig, no demonstrable evidence of interference with intra-auricular conduction.

3. It depresses *A-V* conduction, which, in the dog, proceeds strictly in accordance with other functional changes.

In the late stages of poisoning in the guinea-pig it produces a disproportionately great effect on A-V conduction, leading to 2:1 response of the ventricle, never higher.

4. It produces delay of intraventricular conduction. This is evidenced at first solely by lengthening of the *Q R S* interval, later, by differential widening of the refractory periods of the right and left branches of the *A-V* bundle.

5. It produces remarkable changes in the voltage and sign of the *T* wave. Evidence is found which suggests that these changes are directly related to alterations in intraventricular conduction.

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11. Jackson, Friedlander and Lawrence: J. Lab. & Clin. Med. **7**:311 (March) 1922.

6. It produces, in the dog, a high degree of vagal paresis.

7. It induces death, in dogs, by ventricular fibrillation; in guinea-pigs, by gradual inhibition of the whole heart.

8. Intra-auricular block from quinidin is described in a patient.

9. The clinical use of quinidin in conjunction with digitalis is discussed.

10. Left bundle branch block from quinidin is described in a patient.

11. Some possible relationships of quinidin to sudden cardiac death are pointed out.

AN EXPERIMENTAL AND CLINICAL STUDY OF QUINIDIN SULPHATE: II. CLINICAL*

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CLEVELAND

In the short time that quinidin has been under intensive investigation, a considerable number of facts regarding its action and uses have become generally apparent. It is well recognized that quinidin therapy is not applicable outside the field of disordered cardiac mechanism, and is furthermore limited to two general classes of disorder within that field: (1) The paroxysmal tachycardias, including premature contractions occurring singly or in groups; (2) disorders due to circus movement within the auricle, comprising, (*a*) auricular flutter; (*b*) auricular fibrillation.

Clinical experience with arrhythmias of the first class is still extremely meager. Hamburger [1] mentions a case of auricular paroxysmal tachycardia, but reserves discussion until more extended observations shall have been made. Boden [2] states that quinidin was tried with favorable results in twenty-two cases showing premature beats, mostly ventricular in origin; and that in six cases of atrioventricular or ventricular paroxysmal tachycardia cessation of paroxysms was secured four times, and great diminution of rate twice. White, Marvin and Burwell [1] noted abolition of ventricular premature beats, in one case, during continued medication with small doses of quinidin. Smith [3] reports excellent results in seventeen cases of premature beats and one case of paroxysmal tachycardia. At this point I wish to report a single case.

REPORT OF CASE

History.—(Case 20 [87796]). I. W., a girl, aged 16, had suffered from air hunger on exertion ever since she could remember. After climbing stairs, for example, she felt very dizzy, faint, short of breath and was conscious of unwonted fluttering of her heart. She had never noticed edema. She gave an ample history of previous infections, numbering among them diphtheria, typhoid fever, scarlet fever, measles, pertussis, chronic otitis media, numberless attacks of sore throat, and a questionable story of variola. Clinically, she presented the picture of chronic myocarditis and mitral stenosis, with clearly demonstrable enlargement of both the right and left ventricles and right auricle. The rhythm seemed to be fundamentally under sino-auricular control, but was being con-

* From the Medical Clinic of Lakeside Hospital and Western Reserve University.

1. A detailed list of references will not be attempted. For comprehensive bibliographies see: Hamburger: J. A. M. A. **77**:1797 (Dec. 3) 1921. Oppenheimer and Mann: J. A. M. A. **77**:1800 (Dec. 3) 1921. Wolferth: M. Clinics N. America **5**:783 (Nov.) 1921. White, Marvin and Burwell: Boston M. & S. J. **185**:647 (Dec. 1) 1921.

2. Boden and Neukirch: Deutsch. Arch. f. klin. Med. **136**:181, 1921.

3. Smith: J. A. M. A. **78**:877 (March 25) 1922.

tinually interrupted by premature contractions which occurred sometimes singly, often in small groups, and frequently constituted long paroxysms of tachycardia. The electrocardiogram (Fig. 1) proved the origin of the premature beats and paroxysms to be at the same point in the wall of the right ventricle, and showed that the ectopic impulses were occasionally retrograde to the auricle. The patient was put to bed and quinidin therapy carried out, as follows: December 3, 0.33 gm. (5 grains); December 4, 1 gm. (15 grains); December 5, 1 gm.

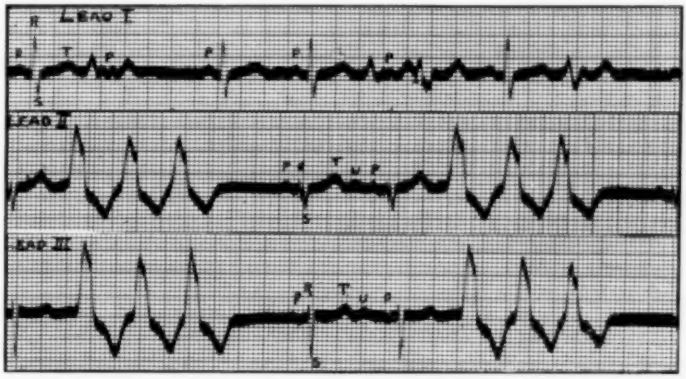

Fig. 1.—Electrocardiogram of I. W. (Case 20, 87796) showing origin of premature beats and paroxysms. In this and all succeeding figures one scale division of abscissae equals 0.04 second, of ordinates, 10^{-4} volt.

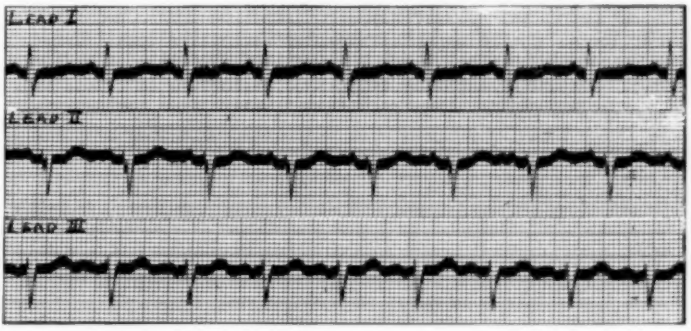

Fig. 2.—Electrocardiogram of I. W. showing absence of premature beats.

(15 grains); December 6, 1.67 gm. (25 grains); December 7, 1 gm. (15 grains); December 8, 1 gm. (15 grains); December 9, 1 gm. (15 grains).

December 7, after 5 gm. of the drug had been taken, the arrhythmia was observed to be absent. Whereas before it had been impossible to secure an electrocardiogram without the appearance of great numbers of the premature beats, it was now easy to do so (Fig. 2). December 9, the efficacy of the treatment was tested by having the patient climb several flights of stairs, immediately after which an electrocardiogram was made (Fig. 3). It will be seen that the paroxysms are prominent. The conclusion was that, although

the paroxysms could be abolished so long as the patient remained at rest, the dosage required to control them during exercise was too high to be practicable in continued use, and the attempt was, therefore, abandoned.

It is probable that disordered mechanism was in this case one of the factors contributing to the patient's disability, but inasmuch as the disability appeared only during exercise, when the tachycardia could not be controlled adequately, the relative contribution could not be gaged accurately. Quinidin directly depresses the excitability of heart

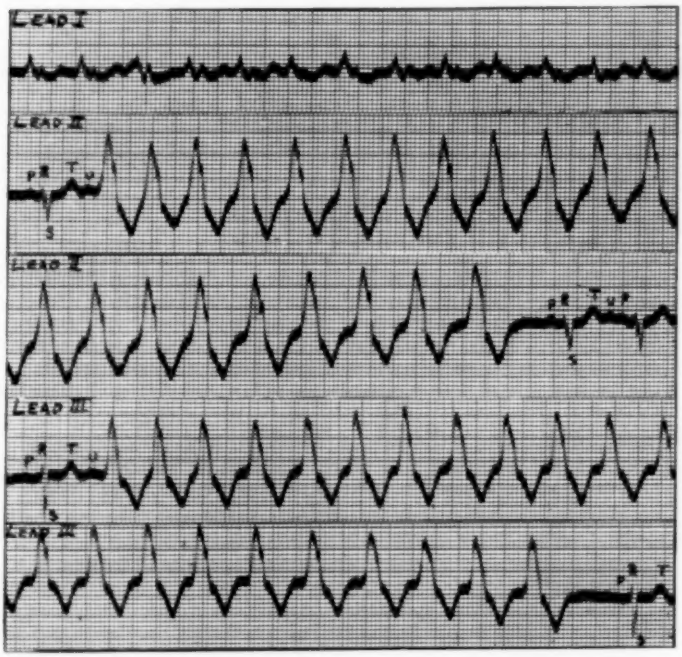

Fig. 3.—Electrocardiogram of I. W. Lead I shows a continuous paroxysm of ventricular tachycardia. Leads II and III show the beginning and end of paroxysms. Rate of tachycardia, 136 per minute.

muscle, and therefore may inhibit any ectopic focus of origin of impulses to a degree sufficient to prevent paroxysms of tachycardia. The action is clearly analogous to the experimental observation, concurred in by most investigators, that the threshold for the production of premature beats or auricular fibrillation is tremendously exalted by quinidin. Failure was encountered in the case described because the heart muscle was not susceptible, within safe limits of dosage, to this action of quinidin. In other cases of similar character the paroxysms

may not only be terminated immediately, but permanently prevented by giving small doses of quinidin. It is obvious that the result can never be predicted in any case.

Certain observations made by Levy [4] are pertinent to this discussion. In one patient he found ectopic ventricular tachycardia occurring among the mechanisms transitional between auricular fibrillation and normal rhythm, and later in the same patient, paroxysms of auricular tachycardia interrupting the established normal mechanism. In other patients ectopic ventricular tachycardia was observed three times. No explanation of this contradictory occurrence suggests itself, unless it be that small doses of the drug may, in certain instances, produce a preliminary lowering of the threshold of excitability, to be succeeded by later exaltation of the threshold under the influence of larger doses.

It is in arrhythmias of the second class, auricular flutter and auricular fibrillation, that quinidin therapy has its widest application. At this point it is necessary to refer briefly to the new theory of circus movement, so ably supported by Lewis and his co-workers.[5] This theory has already been accepted widely; that it will require material revision seems unlikely. By means of it we are made to appreciate the fact that flutter and fibrillation are essentially of the same character, differing only in that in the former the circulating wave of excitation travels always in a constant anatomic path, whereas in the latter it travels on a path which varies in greater or less degree from cycle to cycle. It is to be expected, therefore, that if quinidin modifies the underlying circus movement it will affect flutter and fibrillation in identical ways. This expectation cannot be tested fully until our present acquaintance with the action of quinidin in chronic auricular flutter has been extended considerably. The theory of circus movement is thoroughly competent to explain the mechanism of action of quinidin in abolishing auricular fibrillation [6]—a phenomenon which would otherwise be most obscure. It is remarkable that restoration of a normal cardiac mechanism is secured in almost exactly 50 per cent. of all cases, a fact which of itself strongly suggests that restoration depends solely on some fundamental relation between the action of the drug and the pathologic physiology of the auricular muscle. Conversely, the action of the drug seems to offer additional proof of the theory, for the gradual transition, seen in clinical electrocardiagrams, from fine waved fibrillation through coarse waved fibrillation, impure flutter and pure flutter, to normal rhythm, strongly suggests that fibrillation and flutter are due

4. Levy: Proc. Soc. Exper. Biol. & Med. **19**:88, 1921.
5. Lewis: Heart **7**:127, 131, 191, 247, 293, 1920; **8**:193, 1921.
6. Lewis, Drury, Iliescu and Wedd: Brit. M. J. **2**:514 (Oct. 1) 1921; Heart **9**:55, 1921.

to the same fundamental cause, and that fibrillation is simply an advanced degree of impure flutter.

A review of the literature establishes the fact that in any given case of auricular fibrillation one can never predict whether or not quinidin will be able to restore a normal mechanism, or, once restored, to maintain it. With this fact my own clinical experience with quinidin is in complete agreement. Incidental circumstances, such as the character of the cardiac lesion, the degree of decompensation, the duration of the disordered mechanism, the age of the patient, etc., are not essentially related to failure or success with quinidin. Many examples of this appear among the cases selected for report. If Case 2 be compared with Case 17, one finds that in both patients high arterial pressure was a prominent feature, associated with chronic myocardial disease and chronic nephritis. Case 2 retained auricular fibrillation after 11 gm. of the drug had been given, whereas Case 17 responded with a normal rhythm after 13 gm. The outstanding lesions in Cases 22 and 24 was primary myocardial disease; the former was not affected by 17 gm. of quinidin, but sequential rhythm was easily secured in the latter by 2 gm. Comparison of Case 19 with Case 25 shows that in both cases chronic endocarditis of the mitral valve was present; Case 19 underwent no change in mechanism after 16 gm. of the drug had been given, whereas Case 25 responded with a normal rhythm after the last course of 13.33 gm. In Case 17 auricular fibrillation soon recurred, and normal mechanism was not again restored by 8.33 gm. Case 27, of similar type, responded to the drug with disturbance in intraventricular conduction [7] before any effect on the circus movement was manifest. That fibrillation of very long duration may often be abolished with the greatest ease was well exemplified by Case 24. The disordered mechanism was known to have persisted in this patient for five years, yet a total of 2 gm. of quinidin was sufficient to restore a sequential mechanism. One of the best therapeutic results was secured in Case 14, although the patient declared that he had had an "uneven pulse" for at least ten years. In this patient 5 grains of quinidin every forty-eight hours are sufficient to maintain the normal rhythm, whereas in Case 24 from 15 to 20 grains are required in twenty-four hours. Several of our patients over 70 years of age were among those most susceptible to quinidin therapy. The conclusion of Drury and Iliescu [8] that both successful and unsuccessful cases form heterogeneous groups has become universal.

The outstanding contribution made to clinical cardiology by the introduction of quinidin is the opportunity which it affords of studying

7. This issue, page 32, Figure 45.
8. Drury and Iliescu: Brit. M. J. **2**:511 (Oct. 1) 1921.

quantitatively the rôle of auricular fibrillation in myocardial failure. As clinicians, we have often been at a loss in attempting to evaluate the disordered mechanism. In most instances it has been impossible to determine whether auricular fibrillation was merely one of a number of relatively insignificant details in the clinical picture of cardiac decompensation, or whether it contributed directly to the altered dynamics of the circulation. By means of quinidin we can reach a solution of this problem, for in every case in which auricular fibrillation can be split off by selective drug action from other possible factors in heart failure we are able to gain an unobstructed view of its participation in the production and maintenance of decompensation. We have been provided with a therapeutic test comparable to that which we apply to the problem presented by the patient whose air hunger may be due to pulmonary emphysema, to bronchiolar hypertonus, or to both. If the question cannot be answered by physical signs alone, we may readily solve it by observing the effect of epinephrin on the physical signs, vital capacity, and subjective symptoms. Similarly, if a patient's heart failure be due to high arterial pressure, to auricular fibrillation, or to both, we may evaluate the contribution of the disordered beat by substituting for it a normal cardiac mechanism.

In order to gain a comprehensive conception of the contribution of auricular fibrillation to heart failure it is essential that a normal cardiac mechanism be secured in as many cases as possible. We have already seen that both successful and unsuccessful cases for heterogeneous groups, that the only condition governing restoration of normal rhythm is the susceptibility of circus movement to the action of the drug. Theoretic considerations, therefore, impel us to employ quinidin impartially in all cases of auricular fibrillation. On the other hand, it must be understood, as Hewlett and Sweeney [9] have indicated, that any benefit derived from the use of quinidin is purely the result of a restored normal mechanism, an indirect effect of the drug. Before proceeding further, we must inquire into the nature of the drug's direct effect; and we find that quinidin is a muscle poison which exerts a distinctly depressant action on the myocardium. Whereas digitalis enjoys almost universal application in cardiac failure, the use of quinidin must be restricted not only to those cases of decompensation which have auricular fibrillation, but still further within that group. In every case we must decide as nearly as possible whether the benefit to be expected from resumption of normal rhythm will outweigh the harmful effect of quinidin as a muscle poison. In other words, we must form the best possible qualitative estimate of the extent to which disordered mechanism contributes to cardiac disability; if this is impossible, the only

9. Hewlett and Sweeney: J. A. M. A. **77**:1793 (Dec. 3) 1921.

question remaining for decision before applying the quinidin test is the ability of the myocardium to withstand the temporary depressant action of the drug. Increasing experience with quinidin will help us to make these decisions. From these considerations it is obvious that every patient with cardiac dilatation or stasis of any degree should have the full benefit to his myocardium of digitalis before he is subjected to quinidin.

In order to test the effects of quinidin to the fullest extent, it has been my practice to employ it impartially in all cases of auricular fibrillation, exercising all possible precautions in view of the possible dangers of such procedure. Illustration of some of the points which I have discussed is furnished by one of our patients (Case 3) who had been under intermittent observation for a period of ten years, and was known to be exceptionally prone to acute dilatation of the heart. Slight emotional excitement was alone sufficient to bring on an attack. We were fully cognizant of the advanced state of his myocardial and endocardial involvement, and were convinced that auricular fibrillation was a relatively insignificant feature of his chronic cardiac decompensation. It was confidently predicted that the harmful effect of quinidin as a muscle poison would greatly outweigh any benefit which might be expected from resumption of normal rhythm. Quinidin therapy was three times interrupted by acute dilation of the heart. It cannot be said without qualification that quinidin was the sole cause of cardiectasis, for such an event had been observed numberless times, and was not more frequent or severe during quinidin administration than at other times. On the other hand, it is well to assume, if necessary, that quinidin was at least partially responsible. From this experience several conclusions may be drawn. In the first place, it is perfectly clear that the only important effect of quinidin in this patient was its depressant action on the myocardium. For this reason the experiment was necessarily terminated before any conclusions concerning the rôle of auricular fibrillation could be reached. Pursuing this point still further, however, it is possible that the actual means by which the direct depressant action of the drug was exhibited, rendering decompensation still worse, was the substitution of unaccustomed transition rhythms for an arrhythmia for which, during long sufferance, the myocardium had thoroughly compensated. Eyster and Fahr [10] have called attention to this possibility. There is little doubt that it represents an additional viewpoint from which the clinical use of quinidin must be regarded.

In many patients, however, compensation is not adversely affected by transition rhythms, even if the original arrhythmia is of long standing. As an extreme example, Case 7 may be cited. As far as compensation was concerned it made no apparent difference to this

10. Eyster and Fahr: Arch. Int. Med. **29**:59 (Jan.) 1922.

patient what his cardiac mechanism might be. On several occasions, while maintaining a normal mechanism under the influence of quinidin, he suddenly developed auricular flutter with immediate doubling or tripling of the ventricular rate. These and other changes occurred repeatedly without notice to the patient or modification of his condition. His subjective and objective signs seemed entirely independent of fibrillation, flutter, or normal rhythm. I have had opportunity to observe numerous other cases of similar character.

It remains for us to inquire into the results which may be ascribed to resumption of normal cardiac mechanism. In some cases no beneficial results are evident: either the patient is in worse condition because his myocardium reacted unfavorably to the depressant action of the drug, or to transition rhythms; or his state remains essentially unchanged. In Case 17, for instance, it was demonstrated that a normal rhythm made no perceptible difference in the patient's condition. It might have been possible, but certainly appeared unprofitable, to attempt to maintain the established sinus mechanism. A review of such cases strongly suggests that either auricular fibrillation may exist without in the least embarrassing the circulation, or that the myocardium, having compensated for the embarrassment incurred at the onset of auricular fibrillation, is now indifferent to any alteration in cardiodynamics which may be caused by arrhythmias of this character.

In a considerable number of patients, however, auricular fibrillation is a major factor for producing and maintaining myocardial decompensation, and these patients are tremendously benefitted by permanent restoration of their normal cardiac mechanism. A brilliant illustration is furnished by Case 14. After having been wholly incapacitated for a period of nine months by reason of myocardial incompetence, this patient was rapidly restored to his former vigor and was soon able to resume his duties as a street-car conductor. In perfect comfort he continues regularly at his work fifty or sixty hours a week, and feels that his health is as good as it ever was. His case may be summed up by saying that with auricular fibrillation he is a cardiac invalid, whereas with sinus rhythm he is a healthy man and an efficient economic unit.

Another illustration is recorded in Case 24. This patient had suffered from continuous auricular fibrillation and repeated attacks of severe cardiac decompensation for a period of five years, and his myocardium had never been able to compensate for the disordered mechanism. Although he was brought from a moribund state to a condition of relative comfort by means of digitalis and rest in bed, the last steps in attaining perfect compensation could not be accomplished by these measures. He still retained an annoying sense of precordial distress, and was still unable to lie flat in bed on account of air hunger.

Coincident with the resumption of normal rhythm all remaining symptoms disappeared promptly and completely, and the patient declared that he felt better than at any time in ten years. Under conditions such as these the tendency to recurrence of decompensation is greatly lessened, and the need for continuous digitalis therapy removed entirely.

One who has had opportunity to observe therapeutic successes of so impressive a character will be able to appreciate the great importance of a normal rhythm to numbers of our cardiac patients. Quinidin therapy has already been of such remarkable service in its peculiar field that to render it safe and generally applicable within that field calls for our most earnest efforts.

Brief reference may be made to the possibility of embolism subsequent to restoration of normal mechanism, to which attention has been called by Wilson and Herrmann, Ellis and Clark-Kennedy, Mackenzie, Orr and others. As Wilson and Herrmann [11] have indicated, patients with paroxysmal fibrillation are spontaneously subjected to the danger of embolism. In this connection, therefore, we may consider only the chronic fibrillators, in whom the danger is unquestionably a real one. On the other hand, are the cases of embolism from this cause more frequent than those which commonly occur in fibrillators who are being treated intensively with digitalis, or is it that we hear more of them by reason of the prominence of quinidin in medical literature? It is my belief that the actual percentage of such cases will be found almost equally divided between the two causes. We feel it our duty to extend the benefit of digitalis to our patients, although we realize fully the likelihood of subsequent embolism. Similarly, I believe we shall find it our duty to extend the benefit of a normal cardiac mechanism without probability of greater hazard.

CLINICAL REPORT

Technic.—Quinidin sulphate was administered by mouth in all cases, to the first patient in solution, to all subsequent patients in gelatin capsules, sometimes with the lid of the capsule removed.[12] Approximately sixteen hours after the initial dose of 0.33 gm (5 grains), designed to test the possibility of idiosyncrasy to cinchona, the administration is usually begun with 0.33 gm. four times a day. After a few days this amount is gradually increased if necessary. The largest twenty-four hour dosage was 3.33 gm. (50 grains), and the largest total dosage was 36.0 gm. (545 grains) over a period of twenty days with one intermission of two days (Case 25). Each patient has been

11. Wilson and Herrmann: J. A. M. A. **78**:865 (March 25) 1922.

12. It is worthy of note that Boden [2] has ventured to employ the drug intravenously in doses as high as 0.4 gm. (6 grains). He reports no untoward results from this procedure.

hospitalized for the first course of treatment, but not, as a rule, for subsequent therapy. In view of the known tendency of auricular fibrillation to recur, continuous treatment with quinidin following resumption of normal rhythm is, of course, essential, just as continuous digitalis therapy has been essential in auricular fibrillation. For this purpose the smallest effective dosage is used. It is a curious fact that many workers have expected the sinus mechanism, once restored, to continue indefinitely without support, and have regarded a relapse to fibrillation under these conditions as evidence that treatment with quinidin is a failure. It is to be emphasized that the only important consideration in quinidin therapy is to observe the effect of normal rhythm on compensation over the longest possible period of time.

Unpleasant symptoms attributable to quinidin have been inconspicuous. There were a few instances of headache, tinnitus, fleeting visual disturbance, restlessness, nausea and vomiting, but nothing of an alarming nature appeared except as described in Case 3.

Thirty-six patients have received one or more courses of quinidin. One of these (Case 20) was not a case of auricular fibrillation; three left the hospital before the treatment had been completed. Of the remaining thirty-two cases, twenty (62 per cent.) responded with a normal mechanism. It has been impossible to follow carefully the subsequent course of events in all cases, but it is fairly certain that permanent benefit has been secured in fifteen cases, which is 47 per cent. of the entire series and 75 per cent. of the restored cases.

Electrocardiograms.—These are analyzed in the accompaying table. It will be noted that in several cases the *P-R* interval exceeds the upper limit of normal, but to assume from this that quinidin depresses *A-V* conduction is obviously unjustifiable for the reason that we have no means of knowing the original *P-R* interval. Furthermore, such an assumption means a disproportionately great depression of *A-V* conduction in contrast with other effects, for disturbance of intra-auricular conduction occurred but once and the recorded changes in *Q R S* interval are negligible. That prolongation of the *P-R* interval is extremely unlikely under clinical conditions is apparent from a consideration of the experimental results reported in my preceding paper. Moreover, I have knowledge of one case in which a very long *P-R* interval appeared after the abolition of fibrillation, but reference to a control record, made some time before the original onset of the patient's disordered mechanism, showed this long interval to be the natural one for the patient. The average *P-R* time for the twenty patients is 0.183 second, which might well be the average for a like number of normal hearts.

ANALYSIS OF ELECTROCARDIOGRAMS

Case No.	P-R Time Maximum (Seconds)	QRS Time Maximum (Seconds)	Character of P-wave	Character of T-wave	Voltage of QRS + Increase — Decrease	Remarks
1	0.22	No change	Notching and semi-inversion in Leads II and III	No change	No change	
4	0.16	No change	No change	No change	No change	
5	0.215	Increased by 0.03	Notching in Lead I	Invert to upright in Lead III	— Leads II and III	
6	0.162	No change	No change	No change	+ Lead III	Change from bizarre QRS to notched R, Lead III
7	0.22	No change	No change	No change	+ all leads	
9	0.22	Increased by 0.02	No change	No change	+ all leads	
11	0.21	No change	Diphasic in Lead III	No change	No change	
14	0.20	No change	Notching in Leads I and II; invert and variable in Lead III	No change	— Lead III	Intra-auricular block
16	0.22	No change	No change	No change	+ all leads	S-wave appears in Lead I; character of QRS changed in Leads II and III
17	0.24	No change	Slight notching in Lead II	No change	No change	
18	0.12	Increased by 0.08	Isoelectric in Lead I; invert in Leads II and III	No change	+ all leads	
20	No change	Increased by 0.02	No change	Greatly reduced voltage in Leads II and III	+ Lead II	
21	0.12	No change	No change	No change	+ all leads	
24	0.16	No change	Notched in Leads I and II; diphasic in Lead III	No change	+ all leads	
25	0.18	Increased by 0.02	Isoelectric in Lead I; diphasic in Lead III	Voltage initially reduced, later recovering	No change	
28	0.16	No change	Diphasic in Lead III	No change	No change	
29	0.20	No change	Notched in Lead I; invert in Lead III	No change	No change	
30	0.18	No change	Notched in Leads I and II; diphasic in Lead III	No change	+ all leads	S-wave substituted for R-wave in Lead I
31	0.152	No change	No change	No change	— all leads	
33	0.16	No change	Notched in Lead I; diphasic in Lead III	No change	+ Leads I and III	
35	0.17	No change	Notched in Lead I	No change	— Lead I	

Although notching and semi-inversion of the P wave seem extraordinarily common, deductions therefrom are open to the same criticism as those concerning the *P-R* interval. However, one is probably justified in the belief that the frequent changes in direction and sign of the *P* wave, often conspicuous from beat to beat, which take place for a time after resumption of normal rhythm, are due to instability in location of the pacemaker. Changes in voltage of the initial phases of the ventricular electrocardiogram, occasionally associated with minor alterations in the character of the individual waves, is rather common, but no explanation is forthcoming.

The production by quinidin of undoubted pure auricular flutter at extremely low rates, reaching 130 per minute in one of my patients (Case 8, Fig. 16), is one of the most interesting features from the standpoint of rhythm. It is necessary to revise the old dictum that flutter is unlikely at rates slower than 200 per minute.

PROTOCOLS

Detailed reports of seven successful and six unsuccessful cases from our series are given.

CASE 1 (84011).—A. B., woman, aged 50, had noticed no symptoms of heart disease until March 8, 1921, when she was subjected to a severe fright. Immediately she became conscious of palpitation, tachycardia, and air hunger. Her symptoms progressively increased, and when examined, April 15, she was found to have primary myocardial disease, moderately decompensated, and auricular fibrillation. There was no arterial hypertonus. Patient improved under digitalis, and was not seen again until May 20, 1921, when decompensation was found to have returned. After the physiologic effect of digitalis had been secured, quinidin sulphate, in solution, was given as follows: May 23, 1 gm. (15 grains); May 24, 0.33 gm. (5 grains); May 25, 1.33 gm. (20 grains); May 26, 0.67 gm. (10 grains); total, 3.33 gm. (50 grains); patient vomited some of the drug, so that the exact amount retained is unknown. Normal mechanism became established May 26, and was followed by great improvement in subjective symptoms and possibly lessened cardiectasis. Auricular fibrillation has not recurred and compensation is being well maintained.

CASE 2 (6) (85869).—C. T., man, aged 50, had suffered from air hunger on exertion for ten months. At 36 he had passed through an attack of scarlet fever. Clinically, the picture was that of primary myocardial disease with slight enlargement of both right and left ventricles, and auricular fibrillation. There was no evidence of stasis, hence digitalis was omitted and quinidin therapy immediately instituted as follows: August 4, 1.33 gm. (20 grains); August 5, 1.33 gm. (20 grains); August 6, 2.67 gm. (40 grains); total, 5.33 gm. (80 grains). While the patient was in the act of palpating his radial pulse the evening of August 6, he noted a short period of very rapid rate, suddenly interrupted by a change to slow, regular beating, which continued without further incident. Following the resumption of normal mechanism, the symptoms were wholly alleviated, and the patient was able to continue an active life in perfect comfort, without therapy, for nearly five months. Auricular fibrillation reappeared, Jan. 26, 1922, accompanied by considerable discomfort, and was again abolished by a total dosage of 3.67 gm. (55 grains) of quinidin sulphate. The clinical result was as brilliant as on the former occasion.

CASE 3 (7) (85848).—G. S., man, aged 43, had been incapacitated since 1917 because of air hunger, weakness, edema and ascites. In April, 1920, ten liters

of fluid had been removed from the peritoneal cavity, and there had been many subsequent taps. In September, 1920, the patient was found to be severely decompensated, with extensive cardiac enlargement, auricular fibrillation, tremendous ascites, swollen liver, bilateral hydrothorax, and dependent edema. Rest and thorough digitalization restored good compensation. In August, 1921, the patient presented himself in a condition almost identical with that of the previous year. Rest and digitalis were again effective in restoring compensation. Patient was relieved of 30 pounds of edema and became very comfortable. Physical examination showed extensive symmetrical cardiac hypertrophy, auricular fibrillation, and atrophic cirrhosis of the liver. Synechia cordis was considered a chief factor in the myocardial disease. The blood Wassermann was negative. Quinidin sulphate was given as follows: August 10, 1.33 gm. (20 grains): August 11, 0.33 gm. (5 grains); total, 1.66 gm. (25 grains). Normal rhythm became established August 11, immediately following a pulsus bigeminus of unknown origin. The unstable character of the patient's cardiac mechanism was soon revealed. August 19, three days after discharge from the hospital, auricular fibrillation had returned. Five days later, after 3.33 gm. quinidin had been given, normal rhythm was found to be restored. Thereafter a daily dose of 0.67 gm. was given until September 7. August 31 found the

Fig. 4.—Electrocardiogram of Case 3 (7). Pure auricular flutter. Auricular rate, 250; ventricular rate, 125, per minute.

patient with a normal mechanism, but September 7 an electrocardiogram showed pure auricular flutter (Fig. 4). Quinidin was withdrawn, and two days later fibrillation had returned. Tincture of digitalis was then begun and continued uninterruptedly until September 30, when normal rhythm and digitalis coupling appeared simultaneously (Fig. 5). All medication was then discontinued. Examination October 7 and 14 showed uncomplicated normal rhythm. Similar changes in rhythm were repeated many times in the ensuing months. Although a daily ration of from 1 to 1.33 gm. quinidin might have sufficed to preserve normal mechanism indefinitely, it became apparent that myocardial compensation was entirely independent of rhythms.

Case 4 (14) (83579).—C. M., male, aged 52, suffered severely from acute articular rheumatism at 14, and again at 21, at which time the first symptoms referable to heart disease made their appearance. Aside from slight shortness of breath on exertion, however, the patient remained in good condition until early in 1921, when he became seriously decompensated. Thereafter, he was never free from air hunger, weakness, edema and ascites. He presented the clinical picture of mitral regurgitation, with moderate enlargement, predominantly of the left ventricle, and auricular fibrillation. The latter was known positively since March 25, 1921, but the patient declared that his pulse had been constantly "uneven" for at least ten years. On several occasions rest and digitalis restored a considerable degree of compensation, but he failed to

regain his former comfort and capacity. Finally, after thorough digitalization, quinidin sulphate was given as follows: October 26, 1 gm. (15 grains); October 27, 2 gm. (30 grains); October 28, 2 gm. (30 grains); October 29, 2.33 gm. (35 grains); October 30, 2.67 gm. (40 grains); October 31, 1.33 gm. (20 grains); total, 11.33 gm. (170 grains). Normal mechanism appeared October 31, complicated at first by intra-auricular block[13] and by auricular premature beats. The change to sequential rhythm was signalized by remarkable improvement in the patient's condition, the details of which have already been described. Small doses of quinidin (0.33 gm. in from twenty-four to forty-eight hours) were continued from November 9 to December 21, then omitted. Patient's condition remained unchanged until Jan. 30, 1922, when suddenly the former indefinable uneasiness and lessened capacity returned by reason of reversion to auricular fibrillation. A small amount of quinidin (1 gm.) immediately restored normal rhythm, and, thereby, adequate minute-volume flow of blood. The discomfort disappeared at once and the patient resumed his activities. Since that time he has regularly taken 0.33 gm. quinidin on alternate days, in consequence of which normal mechanism and compensation are perfectly maintained.

Case 5 (17) (87473).—E. H., female, aged 51, weighing 250 pounds, had shown symptoms of myocardial incompetence for three years. She complained of shortness of breath, palpitation, headache, dizziness and slight edema of the ankles. Although the symptoms had gradually increased in severity, there had been no complete cardiac failure. Patient was found to be suffering from severe arterial hypertonus (240/140), chronic myocardial disease with auricular fibrillation and failing compensation, and chronic interstitial nephritis. After considerable improvement had resulted from measures designed to reduce the arterial hypertonus, quinidin sulphate was given as follows:

From November 18 to November 26, 13.00 gm. (195 grains)
From November 29 to December 5, 8.33 gm. (125 grains)

Normal rhythm became established November 26, but soon gave way again to auricular fibrillation which the second course of quinidin failed to abolish. It was determined from subsequent observation that sequential mechanism contributed nothing toward betterment of the patient's condition.

Case 6 (24) (88337).—F. F., a man, aged 65, began to have palpitation and edema in June, 1916. His condition gradually grew worse, and in January, 1917, he was admitted to the hospital in a state of moderate decompensation. He presented the picture of primary myocardial disease with auricular fibrillation, and chronic nephritis. There was extensive enlargement of both right and left ventricles and right auricle. Blood pressure was 135/85. After a month's treatment he was well compensated, and underwent a herniorrhaphy before leaving the hospital. The next cardiac breakdown occurred in 1919, when he spent four months in the Cleveland City Hospital and again recovered good myocardial function. His third experience of heart failure began in 1921, culminating in January, 1922, in his admission to the hospital in a condition of the most extreme myocardial decompensation. Once again there was a prompt response to rest and digitalis, but orthopnea and slight precordial anxiety persisted.

Patient was treated at Lakeside Hospital in December, 1902, for lead poisoning. There was no evidence of heart disease at that time. Although the patient numbers typhoid fever and pneumonia among his past illnesses, and admits that he has been intensively treated for syphilis on several occasions, it is probable that his myocardial disease did not originate from these sources. Auricular fibrillation has persisted for five years. Quinidin sulphate was given as follows: January 20, 0.33 gm. (5 grains); January 21, 0.67 gm. (10 grains); January 22, 1 gm. (15 grains); January 23, 0.33 gm. (5 grains); total, 2.33 gm. (35 grains). Normal rhythm appeared January 22, after 2 gm. had been given. Almost immediately the persisting precordial anxiety and orthopnea vanished, leaving

13. This issue, page 23, Figure 17.

the patient in perfect comfort. It was soon discovered that a daily dose of 1 gm. was the amount required to prevent return of fibrillation. This dosage has been continued for several months with entirely satisfactory results.

Case 7 (25) (88484).—M. C., a man, aged 52, had been perfectly well until late in December, 1921, when he was suddenly seized with precordial pain and extreme air hunger. The symptoms were so severe that the patient was at once incapacitated. The etiology of his heart disease could not be determined from the history. He was found to have chronic myocardial disease with mitral stenosis and auricular fibrillation. There was no demonstrable stasis. The sudden onset of his trouble was interpreted as the result of the initial appearance of auricular fibrillation. Quinidin therapy was carried out as follows:

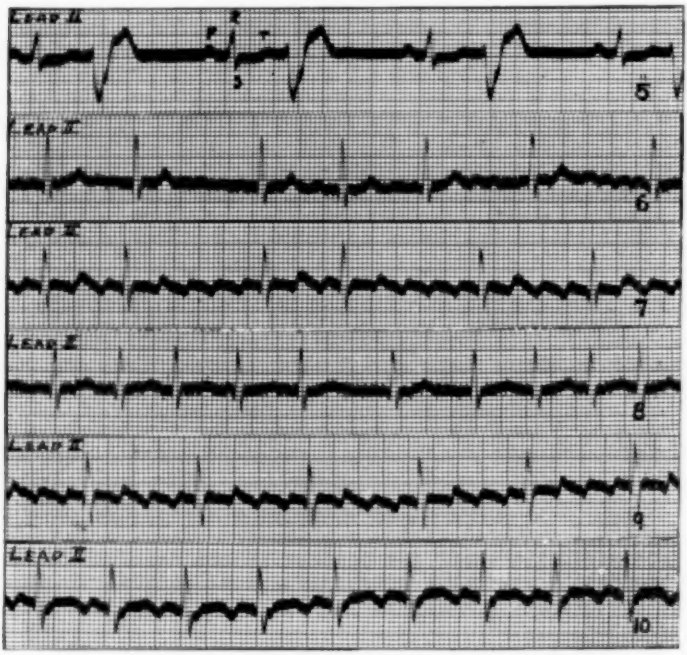

Fig. 5.—Case 3 (7). Electrocardiogram made after digitalization.

Fig. 6.—Electrocardiogram of Case 7 (25) showing auricular fibrillation.

Fig. 7.—Electrocardiogram of Case 7 showing pure auricular flutter. Auricular rate 272 per minute. Ventricle arrhythmic.

Fig. 8.—Electrocardiogram of Case 7 showing auricular fibrillation.

Fig. 9.—Electrocardiogram of Case 7 showing pure auricular flutter. Auricular rate 272, ventricular rate 68, per minute.

Fig. 10.—Electrocardiogram of Case 7 showing pure auricular flutter. Auricular rate 206, ventricular rate 103, per minute.

January 16, auricular fibrillation (Fig. 6); January 23, 1.00 gm. (15 grains); January 24, 1.33 gm. (20 grains); January 25, 1.67 gm. (25 grains); January 26, 1.67 gm. (25 grains), pure auricular flutter (Fig. 7); January 27, 1.33 gm. (20 grains), auricular fibrillation (Fig. 8); January 28, 2.00 gm. (30 grains); January 29, 2.00 gm. (30 grains); January 30, 2.67 gm. (40 grains), pure auric-

ular flutter (Fig. 9); January 31, 2.67 gm. (40 grains); February 1, 2.67 gm. (40 grains), pure auricular flutter (Fig. 10); February 2, 2.00 gm. (30 grains), impure auricular flutter; February 3, auricular fibrillation; February 6, 0.67 gm. (10 grains); February 7, 2.67 gm. (40 grains); February 8, 3.33 gm. (50 grains); February 9, 3.33 gm. (50 grains); February 10, 3.33 gm. (50 grains), normal mechanism (Fig. 11); total, 36.34 gm. (545 grains). The entire medication was carried through without incident. In the ensuing three months small doses (0.33 gm. in from twenty-four to forty-eight hours) have sufficed to maintain normal rhythm. Patient's compensation is constantly good, and he has been able to do light work.

Case 8 (2) (85017).—E. S., a woman, aged 63, had suffered from steadily progressing edema and shortness of breath since January, 1921. In June she was found to be in a condition of severe decompensation, with extensive edema, ascites and air hunger. The clinical picture was that of chronic nephritis, arteriosclerosis of the Gull and Sutton type, chronic myocardial disease and auricular fibrillation. There was considerable enlargement of the right and left ventricles, predominantly the left. Blood pressure was 180/110. After a marked improvement had been effected by means of rest and digitalis, quinidin

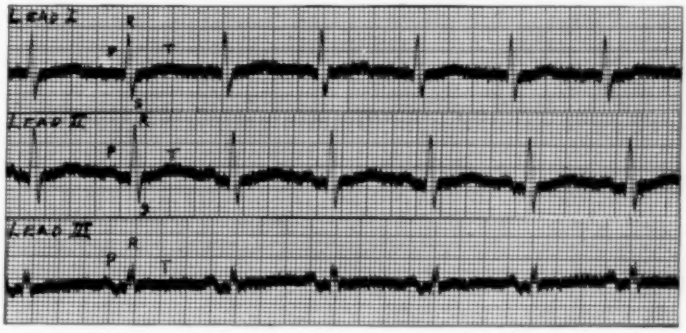

Fig. 11.—Electrocardiogram of Case 7 showing normal mechanism.

was given as follows: June 22, 2.00 gm. (30 grains); June 23, 2.00 gm. (30 grains); July 1, 2.00 gm. (30 grains); July 2, 0.67 gm. (10 grains); July 13, 1.33 gm. (20 grains); July 14, 1.33 gm. (20 grains); July 15, 1.33 gm. (20 grains); July 25, 2.00 gm. (30 grains); July 26, 2.00 gm. (30 grains); July 27, 2.00 gm. (30 grains); July 28, 2.00 gm. (30 grains); July 29, 2.00 gm. (30 grains); July 30, 1.00 gm. (15 grains); total 21.66 gm. (325 grains). The first suspicion that compensation was being unfavorably affected by quinidin was ultimately disproved. During the last course, at the end of which 11 gm (165 grains) had been taken, there were no untoward symptoms. No change in mechanism was effected.

Case 9 (3) (82549).—J. K., a man, aged 41, was suffering from very severe rheumatic endocarditis and myocarditis which had been steadily progressing for thirty years. In May, 1921, he had tremendous cardiac enlargement, very severe stenosis and insufficiency of both the aortic and mitral valves, and chronic auricular fibrillation. The disordered mechanism was a matter of hospital record in 1911. Reference has already been made to the frequency of acute dilatation of the heart in this case. At the time when quinidin therapy was begun the myocardium was in a relatively good state of compensation, that is, the patient was free from edema, there was no demonstrable stasis, and he was perfectly comfortable as long as he remained at rest in bed: May 25, 1.00 gm. (15 grains); May 26, 1.67 gm. (25 grains). Acute dilatation

of the heart occurred May 26; with the help of strophanthin the usual good recovery was made. To comply with the patient's desire, a second attempt was made: June 10, 1.00 gm. (15 grains). This was in turn followed by acute dilatation with good recovery. Finally, at the urgent insistence of the patient, a third course was started. A daily dose of 0.67 gm. (10 grains) was given from August 22 to September 1, inclusive. It was then discontinued for no other reason than severe tinnitus, later being resumed as follows: September 5, 0.33 gm. (5 grains); September 6, 0.67 gm. (10 grains); September 7, 0.67 gm. (10 grains); September 8, 0.67 gm. (10 grains); September 9, 1.00 gm. (15 grains); September 10, 0.67 gm. (10 grains); September 12, 0.33 gm. (5 grains); September 13, 0.33 gm. (5 grains); total, 4.67 gm. (70 grains).

Acute dilatation here made its third appearance, and was again recovered from without serious difficulty. No more quinidin was administered at any time. Patient died more than three months later from acute myocardial failure.

Case 10 (8) (85833).—M. R., a woman, aged 41, was found to be suffering from subacute myocarditis with failing compensation. Her symptoms, which dated from 1917, had become greatly aggravated following an attack of pneumonia in January, 1921. Edema first appeared in July, 1921. Physical examination revealed symmetrical cardiac enlargement of moderate extent, auricular fibrillation (Fig. 12), bilateral hydrothorax, ascites, and dependent edema. Patient was very weak and short of breath. While under observation in the

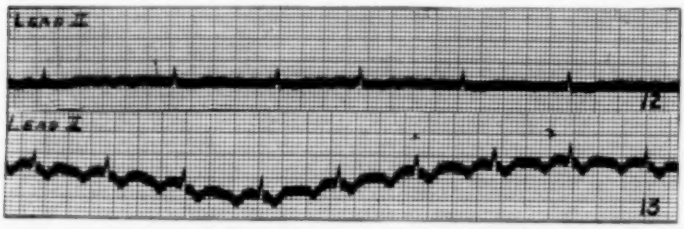

Fig. 12.—Electrocardiogram of Case 10 (8) showing auricular fibrillation.

Fig. 13—Electrocardiogram of Case 10 (8) showing pure auricular flutter. Auricular rate 186; ventricular rate 93 per minute.

hospital she developed mitral stenosis. Quinidin was started while some fluid still remained within the pleural and peritoneal cavities: August 6, 1.00 gm. (15 grains); August 7, 1.33 gm. (20 grains); August 8, 0.67 gm. (10 grains); August 9, 1.33 gm. (20 grains); August 10, 1.33 gm. (20 grains); August 11, 2.00 gm. (30 grains); August 12, 0.67 gm. (10 grains); total, 8.33 gm. (125 grains). Throughout this period compensation certainly did not improve, nor did it become appreciably worse, and there was no change in mechanism. The second trial of quinidin was made after compensation had been well established: August 28, 1.33 gm. (20 grains); August 29, 1.33 gm. (20 grains); August 30, 1.33 gm. (20 grains); August 31, 1.33 gm. (20 grains); September 1, 0.67 gm. (10 grains); September 2, 0.67 gm. (10 grains); September 3, 0.67 gm. (10 grains); total, 7.33 gm. (110 grains). August 31, after 4 gm., the pulse for the first time became regular and rhythmical, but remained fast. An electrocardiogram showed pure auricular flutter (Fig. 13). Massive doses of tincture of digitalis failed to cause reversion to fibrillation. Auricular flutter persisted thereafter for six months, during which time compensation was well supported and the patient comfortable so long as a high degree of *A-V* block was maintained by means of digitalis.

In March, 1922, an effort to carry the mechanism through flutter to normal rhythm was made: March 4, pure auricular flutter (Fig. 14); March 11, 0.67 gm. (10 grains); March 12, 1.33 gm. (20 grains); March 13, 1.33 gm. (20

grains), pure auricular flutter (Fig. 15); March 14, 1.33 gm. (20 grains); March 15, 1.67 gm. (25 grains); March 16, 2.00 gm. (30 grains); March 17, 2.33 gm. (35 grains); March 18, 2.67 gm. (40 grains); March 19, 2.67 gm. (40 grains); March 20, 1.33 gm. (20 grains); March 21, pure auricular flutter (Fig. 16); total, 17.33 gm. (260 grains). March 23, 2.67 gm. (40 grains); March 24, 2.67 gm. (40 grains); March 31, 0.67 gm. (10 grains); April 1, 2.67 gm. (40 grains); April 2, 2.67 gm. (40 grains); April 3, 2.00 gm. (30 grains); total, 13.35 gm. (200 grains). On several occasions the rate of flutter was driven very low, but each time, at the critical point, medication had to be discontinued because of tinnitus, fleeting visual disturbances, nausea and vomiting. Permanent auricular flutter seems to be the final result in this patient, but her condition is no worse than it was with fibrillation.

Case 11 (19) (87641).—T. N., a man, aged 49, began to have symptoms of myocardial weakness in 1914, since which time he had never been free from air

Fig. 14.—Electrocardiogram of Case 10 showing pure auricular flutter. Auricular rate 230 per minute. Ventricle arrhythmic.

Fig. 15.—Electrocardiogram of Case 10 showing pure auricular flutter. Auricular rate 150, ventricular rate 75, per minute.

Fig. 16.—Electrocardiogram of Case 10 showing pure auricular flutter. Auricular rate 130, ventricular rate 65, per minute.

hunger, weakness and edema. He had accomplished only seventeen months' work in seven years. The clinical picture was that of severe synechia cordis, and mitral stenosis of rheumatic origin. There was considerable enlargement of both right and left ventricles, and right auricle, and a very large, vigorously pulsating liver. Blood pressure was 110/70. After compensation had become well established quinidin was given in the endeavor to restore normal rhythm. A total amount of 16 gm. (240 grains) was administered over a period of eight days, without intermission, the maximum daily dose being 2.67 gm. (40 grains). The disordered mechanism was not abolished, and there was no evidence that compensation had been modified in any way.

CASE 12 (22) (87471).—G. N., a man, aged 55, had suffered since 1917, from shortness of breath on exertion and pain in the epigastrium. He had spent much time in hospitals on account of myocardial failure. Physical examination in December, 1921, revealed moderate decompensation with slight dependent edema and left hydrothorax. There was some enlargement of both the right and left ventricles, and right auricle; general arteriosclerosis and auricular fibrillation. Records show that the fibrillation was present in February, 1919. Blood pressure was 130/80. After thorough digitalization, quinidin was given as follows: January 3, 0.33 gm. (5 grains); January 4, 0.067 gm. (10 grains); January 5, 1.33 gm. (20 grains); January 6, 1.33 gm. (20 grains); January 7, 1.67 gm. (25 grains); January 8, 2.00 gm. (30 grains); January 9, 3.00 gm. (45 grains); January 10, 2.67 gm. (40 grains); January 11, 2.67 gm. (40 grains); January 12, 1.33 gm. (20 grains); total, 17.00 gm. (255 grains).

There was no change in mechanism, and no modification of compensation.

CASE 13 (27) (88173).—G. M., a man, aged 65, began to notice unwonted air hunger and weakness in January, 1920. These symptoms grew gradually worse, and several months later edema of the ankles made its appearance. Patient was admitted to the hospital Oct. 25, 1920, in a state of decompensation, with extensive edema and ascites. He presented the picture of chronic interstitial nephritis, chronic myocarditis, and auricular fibrillation. Blood pressure was 180/110. He was discharged Nov. 30, 1920, in a greatly improved condition, and remained fairly well until September, 1921, when the former symptoms returned with renewed intensity. He was readmitted to the hospital Dec. 30, 1921. Prior to admission he had been taking digitalis in sufficient amount to cause characteristic slow bigeminus pulse. In spite of the strong digitalis effect, he had tremendous edema and ascites, swollen liver, and extensive dilatation of the heart. Feb. 1, 1922, all retained body fluid had been eliminated and compensation satisfactorily reestablished. Quinidin sulphate was given as follows: February 6, 0.33 gm. (5 grains); February 7, 1.33 gm. 20 grains); February 8, 2.00 gm. (30 grains); February 9, 2.00 gm. (30 grains); February 10, 2.00 gm. (30 grains); February 11, 1.00 gm. (15 grains) total 8.67 gm. (130 grains). The auricular fibrillation was not abolished, but February 10, after 6 gm. of the drug had been taken, the electrocardiogram showed left bundle branch block.[13] Quinidin was withdrawn, and February 13 the branch lesion had completely disappeared.[14]

SUMMARY AND CONCLUSIONS

1. The result attained by the use of quinidin in a case of ventricular paroxysmal tachycardia is described. The manner in which the drug acts in cases of this character is discussed.

2. Clinical evidence is presented which lends support to the theory that the action of quinidin in abolishing circus movement is not conditioned by the type of cardiac lesion, degree of decompensation, duration of fibrillation, etc., but is essentially related to the pathologic physiology of the auricular muscle.

3. The most important contribution of quinidin to clinical cardiology is that it provides a means by which the rôle of auricular fibrillation in myocardial failure may be quantitatively estimated.

4. Quinidin is universally a heart muscle poison. In each patient an estimate of this effect must be carefully weighed against the expec-

14. This issue, page 32, Figure 46.

tation of benefit to be derived from restoration of normal sinus mechanism. Indications for the use of digitalis and quinidin are entirely separate and clearly defined.

5. The effect of restored normal cardiac mechanism on compensation is illustrated by presentation of cases.

6. Electrocardiograms made before and after resumption of normal rhythm are analyzed.

ON THE TECHNIC OF THE DETERMINATION OF THE VELOCITY OF THE ARTERIAL PULSE WAVE *

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As early as the third century B. C., there was a conception in Greek medicine (Erasistratus) that the pulse in the parts of the body nearest the heart appeared earlier than at the extremities. This conception seems to have been forgotten until 1734, when it was emphasized again by Weitbrecht.[1] The first to measure the time difference in the appearance of the pulse in the central and the more peripheral arteries was E. H. Weber,[2] in 1850. Weber used palpation of the pulse, and took the time on an ordinary watch. He found by this means that the pulse wave in the dorsal artery of the foot appeared later than the pulse wave in the external maxillary artery. A few years after that, Vierodt,[3] in Germany, and Marey,[4] in France, introduced the sphygmograph. In 1861, Buisson [5] did the first determinations of the velocity of the pulse wave by means of a graphic method. He used two Marey tambours; one was applied to the proximal part of an artery, and the other to a more peripheral part. The motions caused by the pulse wave were conducted by means of air to two other tambours, to which small levers were attached. The movements of these levers were registered on smoked paper on the same rotating cylinder. The following methods, including ours, can be considered as developments of the Buisson principle; they differ in respect to the manner in which the movements of the arterial wall are transmitted, and in respect to the manner in which these movements are recorded.

After having tried different methods, Czermak,[6] in 1864, devised a method, which, in its main features, was the same as Buisson's. In 1872, Landois [7] transferred the movements of the pulse to the smoked paper by means of electromagnets. Grummach,[8] in 1879, tried Landois'

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1. Weitbrecht, J.: (Cited from Landois.) Comm. acad. imper. scient. Petropol. 1734-1735, p. 317.

2. Weber, E. H.: Berichte über die Verhandl. Königl. Sach, Geschellsch. d. Wissensch. Math.-phys., Classe 1850 **3**:196, 1851.

3. Vierordt, K.: Die Lehre vom Arterienpuls in gesunden und kranken Zuständen gegründet auf einer neue Methode der bildlichen Darstellung des mench. Pulses, Braunschveig, 1855, p. 56.

4. Marey: Recherches sur le pouls au moyen d'un nouvel appareil enregistreur—le sphygmographe, Paris, 1860.

5. Buisson, P. C.: Gaz. méd. **20**:319, 1861.

6. Czermak, Y. N.: Prager med. Wchnschr., No. 17, 1864 (cited after Landois).

7. Landois, L.: Die Lehre vom Arterienpulz, Berlin, p. 294, 1872.

8. Grummach, E.: Arch. f. Anat. u. Physiol. (Physiol. Abteil), p. 416, 1879.

method, but found that it had too many possibilities of error; and he himself devised a method, which in its main features corresponded to Buisson's, but in which an improved method of time marking was employed. The Buisson-Grummach method became the standard method used in studies of the velocity of the pulse rate in the following period. It seems easy, but it has, however, several difficulties, particularly in the adjustment of the levers to the smoked paper. If they are too tight, the movements are hampered; and if they are not tight enough, the recording of the movements is unsatisfactory. It is furthermore necessary to have the points of the levers in perpendicular lines (one above the other); if they are not, it is necessary to determine the horizontal distance between them, which is not always possible. Ruschke [9] tried to avoid these difficulties by a photographic record of the movements of the levers. His method is rather difficult to use, because it requires that the work be done in the dark.

An extensive historical review of the technic has been made lately by Laubry, Mougeot, and Giroux.[10] These investigators themselves use the Buisson-Grummach method. In 1920-1921 the hot wire apparatus was introduced into medicine (Tucker;[11] Hill[12]) for registration of pulse and heart beat and of movements of similar kind. The oscillations of a string which is a part of a Wheatstone bridge, are recorded on an electrocardiograph. It moves when it is cooled from the puff of air caused by the movement of the skin over the vessel. The stream of air is conducted through a rubber tube. In 1921 it was applied by Hill[13] to a determination of the velocity of the pulse wave, and in 1922 Bramwell and Hill[14] published a few determinations on patients. By this method extremely beautiful curves of the pulse are obtained. We think, however, that the usual transmission by means of rubber tubes and tambours is more practical for ordinary clinical purposes than the vary ingenious hot wire method, and it does not seem to be less accurate if the rubber tubes are of equal lengths and the tambours equally moveable.

It had also occurred to us,[15] in attempting to study the velocity of the arterial pulse wave, that the camera of the electrocardiograph might

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9. Ruschke, K.: Beitrag zur Lehre von der Fortplanzungsgeschwindigkeit der Pulswellen bei gesunden und kranken Individuen, Dissert., Jena, 1912.

10. Laubry, Ch.: Mougeot, A., and Giroux, R.: Arch. d. mal. du coeur **2**: 49, 1921.

11. Tucker, W. S., and Paris, E. T.: Phil. Tr. Roy. Soc. London **221**:389, 1921.

12. Hill, A. V.: Lancet **2**:752, 919, 1921; J. Physiol. **54**:53, 1920.

13. Hill, A. V.: J. Physiol. **54**:119, 1921.

14. Bramwell, J. C., and Hill, A. V.: Lancet **2**:891, 1922.

15. A preliminary report of our procedure has been given in the Danish Society for Internal Medicine, April, 1921, and in Compt. rend. Soc. de biol. **84**:371, 1921.

be employed to record the curve obtained from the arteries. The use of this apparatus made it possible, at the same time, to inscribe the electrocardiogram.

The procedure adopted is as follows: Two arterial pelotes are applied as usual, one to the carotid, and one to the radial artery. Two rubber tubes of equal length transmit the movements of these pelotes by air to two tambours, so placed on an appropriate support, that the recording levers are from 20 to 30 cm. from the narrow slit of the camera of the electrocardiograph, between it and the light system. The time is recorded in the manner usual in taking electrocardiograms. As the slit is very narrow, the parts of the levers which are recorded, are always focussed to points which lie on the same ordinate, that is to say, on a line perpendicular to the direction of movement of the photographic plate, and parallel to the time lines. In this way the difficulties involved in using smoked paper are avoided, as well as the very considerable inconvenience of working in the dark, as is done in the Ruschke method.

As a matter of fact, the electrocardiograph is not indispensable. Any camera, in which the sensitive surface moves at a uniform and sufficiently rapid rate, a chronograph and a light source of great intensity with a system of lenses for projecting the light on the slot of the photographic chamber, for instance Frank's kymographion,[16] will answer the purpose. The electrocardiograph is preferable, however, when it is available, because it makes it possible to record the electrocardiogram at the same time as the two arterial curves. This arrangement has the advantage of indicating to what heart contraction a given pulse wave corresponds, a very useful correlation in the study of the velocity of arterial waves in patients presenting various forms of arrythmia, and on the much discussed subject of the velocity of the large and small arterial waves, as in pulsus altermans, and in pulsus bigeminus of extrasystolic origin. The photographic plate, or film, must move with a speed two to three times that employed for recording electrocardiograms.[17] The foot points of the arterial waves must be clearly defined. This is a point which is not always obtained by using ordinary pelotes. The pelote which is placed over the radial artery is of the spring variety used by Mackenzie. It is fastened on the cross piece which connects two pieces of wood. To prevent this support from slipping, there are fastened to the under surface of the parallel pieces of wood, strips of rubber which are triangular in cross section. In the free space between these, the knob of the pelote falls.

16. Frank, O.: Technik u. Methodik, Ztschr. f. biol. **1**:105, 1908.
17. More often it is well to use a speed of 4 meters per minute.

The carotid receiver (Fig. 1) is an ordinary metal tambour. To the center of the rubber membrane is fastened a small metal knob to be applied to the artery.[18] This tambour has a rather long shank. This portion of the apparatus rides inside a cylinder, the shank of the tambour passing through an opening at the upper end. A slot is cut in one side of the cylinder, through which passes a thread rod from the tambour. The nut on that rod serves to fasten the tambour in position. There is a spring on the shank which presses the head of the tambour against the artery. This tambour corresponds, as will be seen,

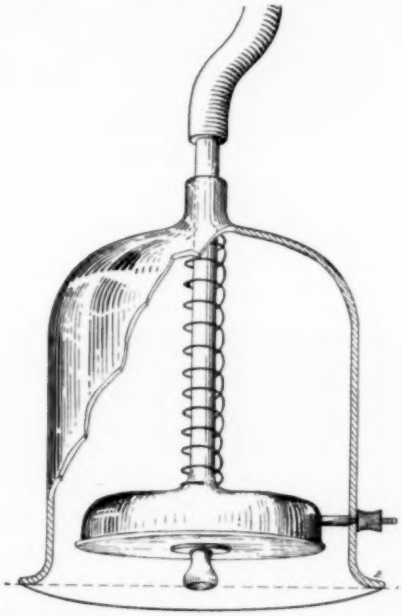

Fig. 1.—Carotid receiver. The tambour can be moved up and down, and fastened in a given position by means of a screw at the side.

rather closely to Marey's "explorateur a coquille ou a resort," and to Brondgeest's pansphygmograph.[19] By this means, appropriate pressure against the soft part of the neck is obtained. The curves obtained with this equipment are read with a precision of from 1/125 to 1/150 of a second without the aid of any auxiliary apparatus. The interval

18. By using this receiver no disturbing influence, from the waves in the jugular vein is seen.

19. Brondgeest, P. Q.: Onderzoekingen gedaan in het Physiologisch Laboratorium der Utrechsche Hoogeschool **2**:326, 1873.

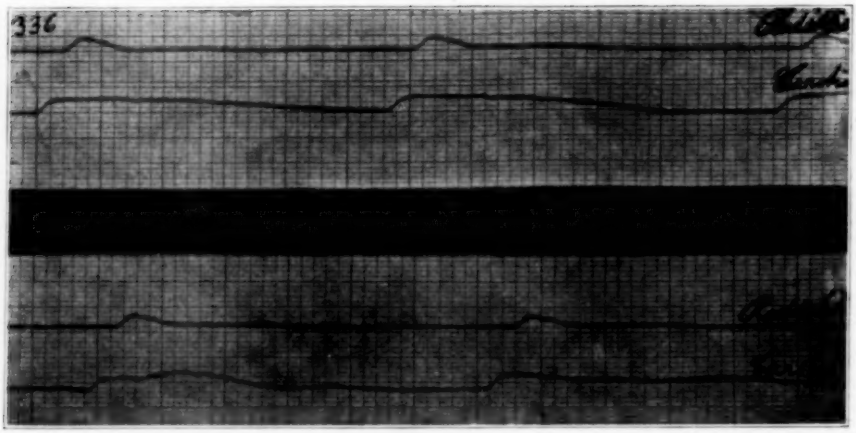

Fig. 2 (Plate 336).—Curves of a normal person. Above, the curve of the radial artery; below, of the carotid artery. Speed of photographic plate, 3.8 meters a minute. The duration between the ordinates equals 0.04 second. The time interval between appearance of carotid and radial waves is of normal length ($\frac{2}{25}$ of a second).

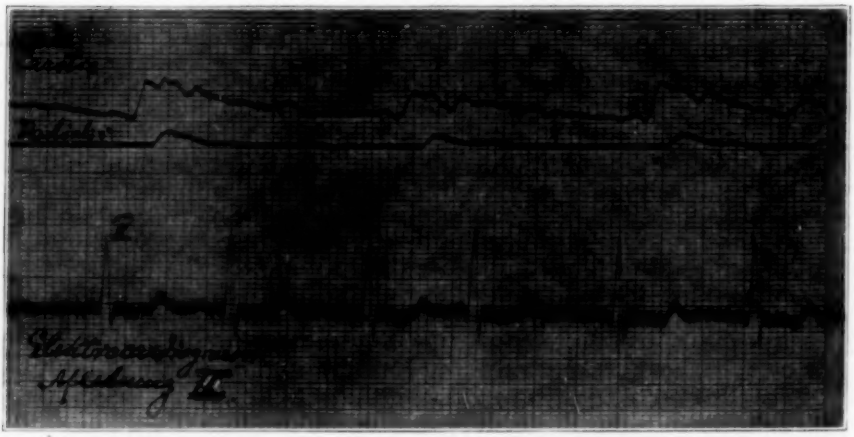

Fig. 3 (Plate 380).—Curve of carotid and radial and electrocardiogram recorded simultaneously on a patient showing auricular fibrillation and perpetual arrhythmia. Speed of photographic plate, 2.5 meters per minute. Interval between carotid and radial waves normal. Note that a certain number of heart beats are missing in the arterial system. The contraction of the heart indicated by an X in the electrocardiogram gives only an indistinct wave in the carotid, and practically none in the radial. In this way the pulse deficit (Robinson and Draper) is recorded graphically.

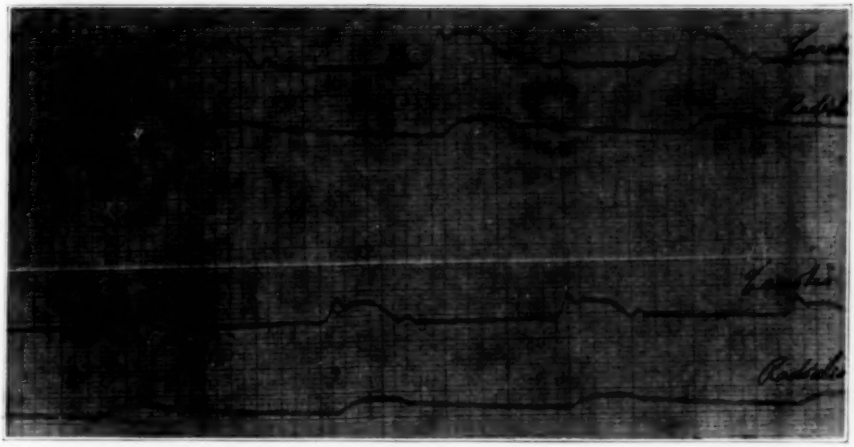

Fig. 4 (Plate 289).—Curves from a patient suffering from chronic nephritis and arterial hypertension. Speed of photographic plate, 3.9 meters per minute. The time interval between the carotid and radial upstroke is $\frac{1}{25}$ of a second, which is about one half of that normally found.

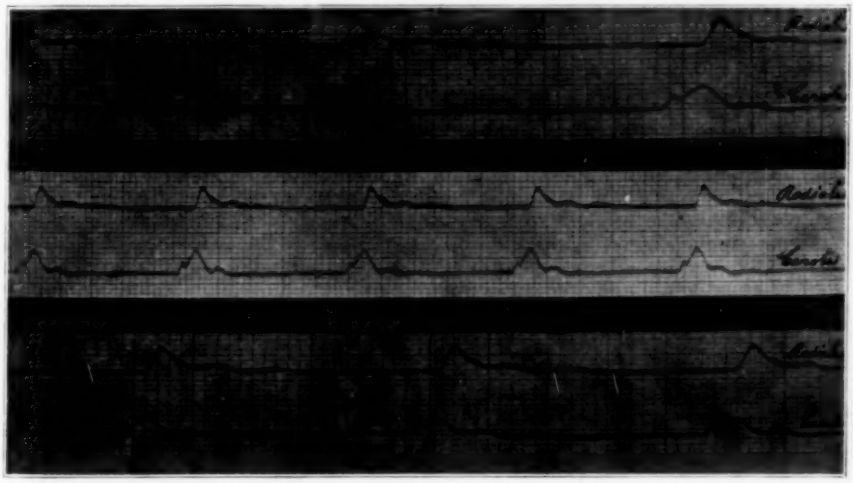

Fig. 5 (Plate 413).—Three pairs of curves from a 28 year old patient suffering from aortic and mitral insufficiency. The time interval between carotid and radial waves is normal. The speed of plate, 4.2, 3.4 and 1.95 meters per second, respectively.

separating the appearance of the two arterial waves being usually about 2/25 of a second in a normal individual, the error of the method will be about 10.5 per cent.[20]

In Figures 2, 3, 4 and 5, are reproduced some examples of curves recorded by this method. The results of a rather large series of experiments on healthy persons as well as on patients, will be published later.

20. Hermann, L.: Handb. d. Physiol. **4**:189, 1880.

THE RELATION BETWEEN INGESTED FAT AND THE LIPEMIA OF DIABETES MELLITUS *

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Since patients with diabetes mellitus are more dependent on fat as a source of energy than are normal subjects, it is tempting to try to explain the hyperlipoidemia that is so common in this disease on the basis of some theory that assumes a relationship between the amount of fat in the food and the percentage of lipoids in the blood. In the literature that has accumulated on this subject a tendency to assume this relationship is evident. In the Rockefeller monograph,[1] for example, the authors state that lipemia "is largely associated with the fat intake and with other diabetic symptoms." Ervin [2] states that "the lipemia of a diabetic will disappear with the elimination of fat from the diet." Bang [3] believed that the lipemia was, in part, alimentary. Joslin [4] suggests a relation between the high protein, fat diets of former days and the high degrees of lipemia reported, and states that "with restricted diet, particularly of fat, the blood fat rapidly falls." Bloor [5] has recently supported a suggestion of Allen's [6] that there is lacking a pancreatic hormone which is necessary for the proper removal of the fat from the blood. Bloor continues by conceiving that the factor of overwork must be taken into consideration in examining into the cause of diabetic lipemia, and that the patient has a fat tolerance which can be raised or lowered according as the ingested fat is restricted or increased. When large amounts of fat are ingested, the mechanism for the utilization of fat might be expected to break down, and he reported a case in which he alleges that a high lipemia resulted from a dietetic indiscretion which consisted chiefly in the ingestion of milk and cream.

In view of this belief, it was thought desirable to note the effect on the lipoidemia of diabetic patients of the high fat, low protein, low carbohydrate diets described by Newburgh and Marsh.[7] Since in these

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1. Allen, F. M.; Stillman, E., and Fitz, R.: Total Dietary Regulation in the Treatment of Diabetes, Monograph of the Rockefeller Institute of Medical Research, No. 11, 1919, p. 143.
2. Ervin, D. M.: Relation of Glycogen to the Pathologic Changes in Pancreatic Diabetes, J. Lab. & Clin. Med. **5**:146, 1919.
3. Bang, I.: Diabetic Lipoidemia, Biochem. Ztschr. **94**:359, 1919.
4. Joslin, E. P.: Diabetes Mellitus, Oxford Med. **4**:146, 1921.
5. Bloor, W. R.: Lipemia, J. Biol. Chem. **49**:201, 1921.
6. Allen, F. M.: Rôle of Fat in Diabetes Mellitus, Am. J. Med. Sc. **143**: 313, 1917.
7. Newburgh, L. H., and Marsh, P. L.: The Use of a High Fat Diet in the Treatment of Diabetes Mellitus, Arch. Int. Med. **26**:647 (Dec.) 1920.

diets the great majority of the calories are derived from fat, and since in each case the caloric requirement of the patient has been satisfied, the daily fat intake is relatively high, usually in the neighborhood of 4 gm. per kilogram of body weight. This is more fat than is ordinarily consumed by the normal subject, and it seems certain that if there were a defect in the metabolism of fat similar to that in the metabolism of carbohydrate, a hyperlipoidemia must result. This should be particularly true in those subjects who demonstrated their tendency to hyperlipoidemia by presenting on admission to the hospital a gross increase over normal in their blood lipoids.

The patients selected for this study represented a number of different types of diabetes mellitus, varying in age, severity of the disease, duration of diabetic symptoms, previous treatment, degree of acidosis. The total lipoids of the blood were determined by the method of Bloor [8] which may be considered sufficiently accurate for comparative purposes and which would certainly demonstrate any large changes in lipoidemia.

REPORT OF CASES

Case 1 (21-276).—An American farmer, 22 years of age, entered the hospital Feb. 7, 1921, complaining of polyuria, weakness and loss of weight. A brother died of diabetes at 17. His past history is of no importance. His best weight was 164 pounds just before the onset of his diabetes; his weight at admission was 127 pounds. His symptoms appeared abruptly in August, 1920, and the diagnosis was made by his physician immediately. His diet was moderately restricted and he continued to lose weight and strength. Except for septic tonsils his physical examination was negative.

On a diet containing protein, 20 gm.; fat, 85 gm.; carbohydrate, 14 gm., and 900 calories, his urine became sugar-free on the fourth day, ferric chlorid reaction negative on the ninth day and his blood sugar normal on the sixteenth day. His diet was gradually increased until he was receiving daily protein, 43 gm.; carbohydrate, 25 gm.; fat, 230 gm., and 2,350 calories. This allowed him 3.9 gm. fat per kilogram of body weight per day.

It will be noted from Chart 1 that his lipemia, which amounted to between 8 and 9 per cent., gradually fell and was still falling up to the time of discharge, in spite of the fact that he was eating large quantities of fat. The curve of his blood lipoids present three phases: A slow fall for about twenty-five days, a rapid fall during the next ten days and a slower fall during the remaining period. It is interesting to note that his food became sufficient to supply his caloric requirement at the beginning of the period when the fall in fat was most rapid; this was demonstrated by the cessation of loss of weight and the establishment of nitrogen balance.

Case 2 (21-321).—An American farmer, 28 years of age, entered the hospital March 1, 1921, complaining of the usual diabetic symptoms. There was no family history of diabetes, except that a 4 year old son of his had had an occasional glycosuria. There was nothing of importance in his past history. Polyuria, polydipsia and polyphagia developed in August, 1914, when the patient was 21. During the following three months his weight fell from 160 to 113 pounds.

Treatment was not started until January, 1915. Four days of complete starvation followed by several days during which he was allowed green vegetables and two or three more days of starvation, a total of ten days, rendered

8. Bloor, W. R.: J. Biol. Chem. **23**:317, 1915.

his urine sugar free. He was discharged on a diet which allowed him considerable freedom in the kinds of the foodstuffs that he ate but which was very much restricted in total calories. During the following two years he felt fairly well most of the time, although he had sugar in his urine frequently. Between the spring of 1916 and March, 1921, he was not free from sugar at any time, in spite of the fact that he was starved on five occasions for periods of from four to ten days.

During the month preceding his admission to our ward he suffered from epigastric distress, "heart burn" and nausea. His symptoms were sufficiently severe to make his home physician suspect peptic ulcer. His vision had failed

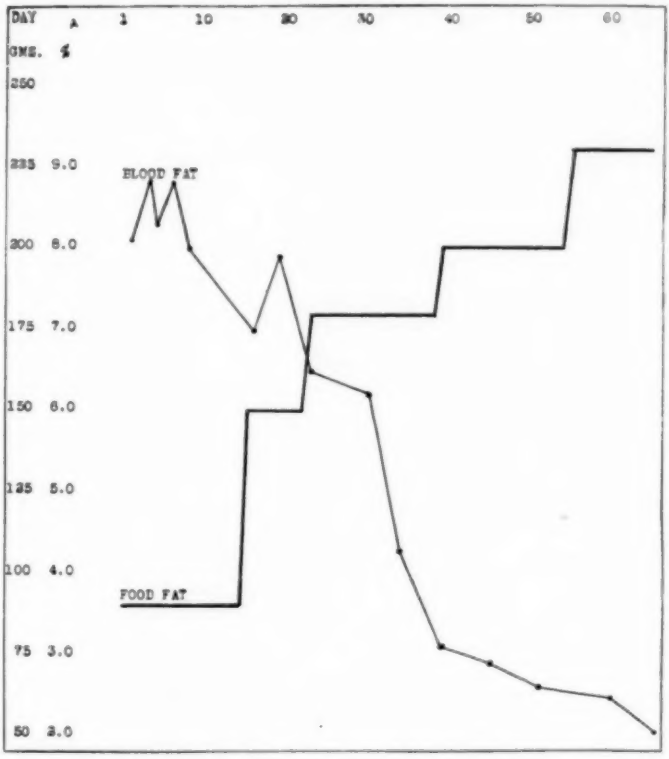

Chart 1.—Graphic chart from Case 1.

and he was badly constipated. On examination it was noted that he was decidedly stuporous and went to sleep while his blood was being taken for the laboratory examinations. Later he could not remember anything that had happened during the first day he was in the hospital. His breath had a decided acetone odor. His right knee jerk could be obtained only on reenforcement, and his left could not be obtained at all. His urine contained a trace of albumin, reduced Fehling's solution, and gave a heavy reaction with ferric chlorid. His blood sugar was 0.38 per cent. and the carbon dioxid combining power of the blood plasma by the Van Slyke method was 37 volume per cent.

On a diet containing, protein, 20 gm.; fat, 90 gm.; carbohydrate, 14 gm., and 950 calories, there was a rapid relief of his acidosis, as shown by the rise in the carbon dioxid combining power of the blood plasma and the disappearance of the ferric chlorid reaction. There was no glucose in his urine on the eleventh day. His diet was increased until he was receiving, protein, 43 gm.; fat, 220 gm.; carbohydrate, 11 gm., and 2,200 calories. While the initial hyperlipoidemia in this case was not as marked as in Case 1, it was definite, and

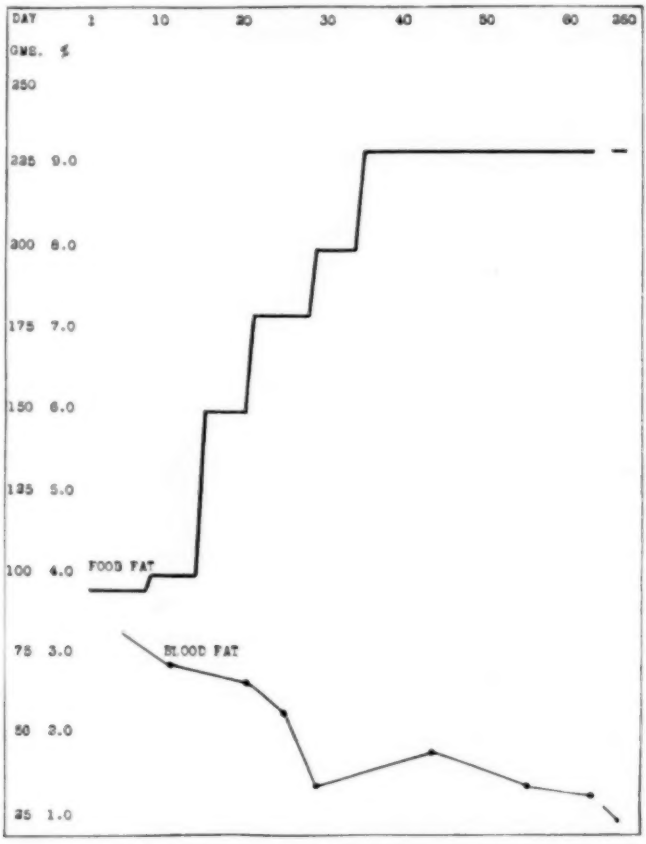

Chart 2.—Graphic chart from Case 2.

the determinations were made over a much longer period of time, there being nearly nine months between the first and last blood lipoid record. The fall was from about 3.3 to 1 per cent.

Case 3 (21-678).—An American clerk, 19 years of age, entered the hospital March 24, 1921, complaining of the usual diabetic symptoms. There was no history of diabetes in the family and nothing of importance in his past history. The disease had developed abruptly fifteen months before, and during the first three months he lost 30 pounds in weight. In spite of severe restriction in his diet, there was no improvement in his symptoms. Twelve days before

he came to us he was starved for seven days but did not know whether he became sugar-free. There had been some numbness of his feet and for two months he had had boils on his legs. On examination, evidence of advanced bilateral pulmonary tuberculosis was found and this complication was confirmed by roentgenograms and sputum examination.

There was no acidosis at any time, and the urine became sugar-free on the third day. The fall in blood lipoids as the food fat was increased is shown in Chart 3. The diet of the last period recorded on the chart contained, protein, 30 gm.; fat, 180 gm.; carbohydrate, 15 gm., and 1,800 calories, which allowed him 4.3 gm. of fat per kilogram of body weight.

Case 4 (21-1392).—An American merchant, 35 years of age, entered the hospital May 19, 1921, complaining of loss of weight, weakness, polyuria and

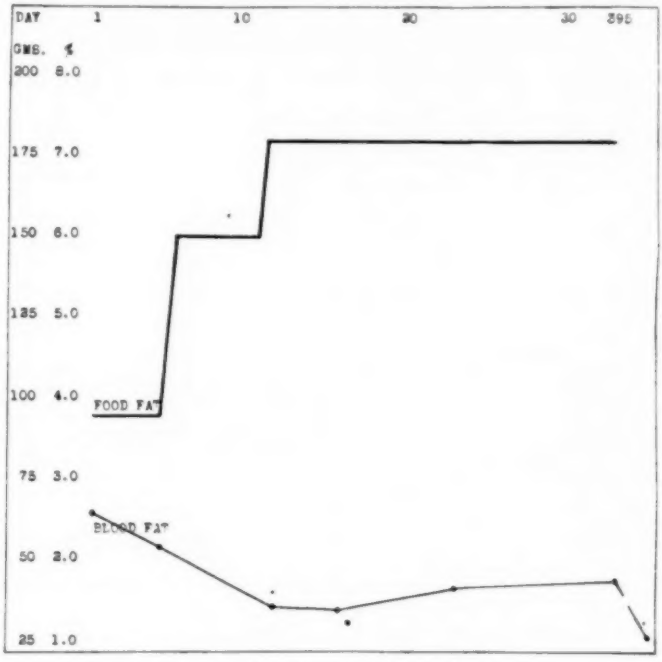

Chart 3.—Graphic chart from Case 3.

polydipsia. His symptoms developed abruptly in January, 1918, when he was 32 years of age. Glycosuria was found, and he became sugar-free on a rather liberal diet. After a few weeks he was advised to return to a normal diet; symptoms and glycosuria promptly reappeared. He again became sugar-free on the liberal diet and adhered to it about a year.

During the following year he increased his food intake and frequently found sugar in his urine. During this second year of his diabetes he had frequent night sweats, with one attack of pain in the lower left chest lasting some weeks. In February, 1920, he had influenza, and during the next few months his weakness progressively increased. In the fall of that year he spent four weeks in a sanitarium, and was discharged on a diet that was liberal, including a large quantity of gluten bread. From that time he grad-

ually went down hill, and since February, 1921, he had not been able to work. During the course of the diabetes his weight had fallen from 120 to 85 pounds. Physical and roentgen-ray examination demonstrated pathology in both pulmonary apices but no sputum could be obtained.

On a diet containing 20 gm. protein, 90 gm. fat, and 14 gm. carbohydrate he became sugar-free on the eleventh day and the ferric chlorid reaction of his urine became negative on the fourteenth day. A moderate acidosis, demonstrated by the lowered carbon dioxid combining power of the blood plasma was promptly relieved. There was a gradually increasing edema during the first two weeks of treatment. His fat intake during the last period before discharge amounted to 3.8 gm. per kilogram of body weight. The fall in total lipoids of the blood is shown in Chart 4.

Case 5 (21-3458).—American, farm hand, 17 years of age, entered the hospital Nov. 26, 1921, with a diabetes that had appeared abruptly in June of the same year with polyuria and weakness. In the interval his weight had fallen from 140 to 125 pounds. His family and past histories are of no importance.

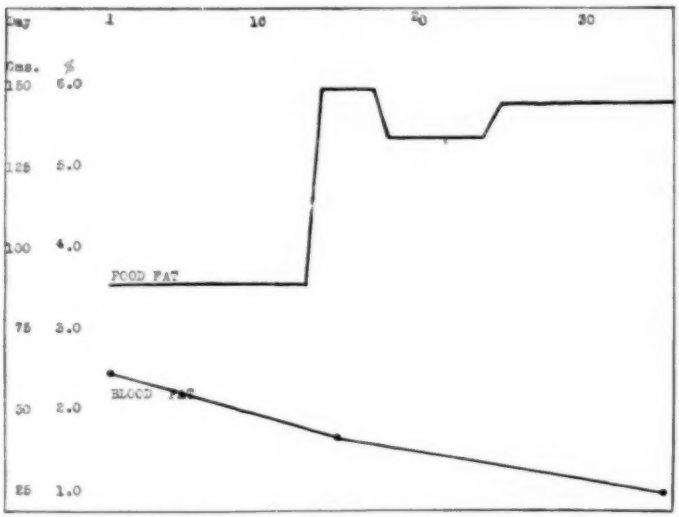

Chart 4.—Graphic chart from Case 4.

No significant abnormalities were noted in his physical examination. On a diet containing 19 gm. protein, 88 gm. fat, and 13 gm. carbohydrate his urine became sugar-free on the eleventh day and the ferric chlorid reaction was negative on the seventh day. His diet was increased until he was receiving, protein, 55 gm.; fat, 200 gm.; carbohydrate, 30 gm., and 2,150 calories. At his weight of 121 pounds, this represented 3.6 gm. fat per kilogram of body weight. His lipoidemia, which was not elevated at the beginning of treatment, remained at the same level throughout.

Case 6 (21-2418).—An American housewife, 22 years of age, entered the hospital Aug. 25, 1921, complaining of weakness and frequency of urination. Her family and past history was of no importance. Eight weeks before she went to her physician because of pain in the bladder and frequency of urination. Sugar was found in her urine. Weakness had been progressive and her weight fell from 120 to 93 pounds. Constipation had been obstinate. Nothing of importance was noted in the physical examination. The blood Wassermann and blood count were normal.

On a diet containing, protein, 18 gm.; fat, 90 gm.; carbohydrate, 13 gm., her urine was sugar-free on the fourth day; the ferric chlorid reaction was negative throughout. She was discharged from the hospital September 14 with a diet containing protein, 55 gm.; fat, 220 gm., and carbohydrate, 25 gm. She remained sugar-free until the latter part of December when she returned to the hospital because of the reappearance of sugar in her urine.

On this occasion she became sugar-free in twenty-four hours, and her diet was rapidly increased to its former level. The blood lipoid determinations were made during this period. It will be seen from Chart 6 that four months of a diet rich in fat did not increase her lipoidemia above the normal level. Two hundred and twenty grams of fat at a body weight of 100 pounds represents 4 gm. of fat per kilogram of body weight.

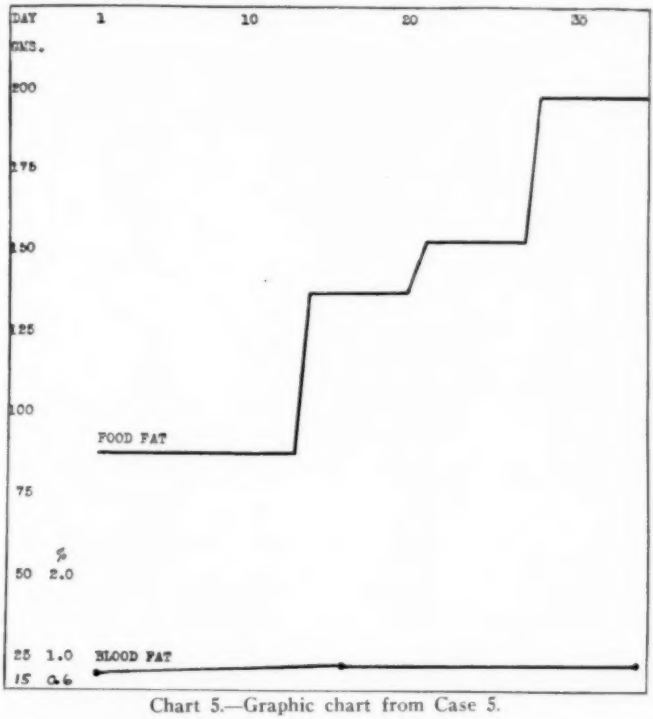

Chart 5.—Graphic chart from Case 5.

CASE 7 (22-2).—An American housewife, 47 years of age, entered the hospital Jan. 2, 1922, with diabetes that had developed abruptly with cramps in the legs and polyuria in December, 1920. Glycosuria was found by the physician. Her weight had fallen from 168 to 121 pounds. Treatment had consisted of strict limitation of carbohydrate which did not keep her urine sugar free. Nothing of importance was noted on physical examination. On a diet containing 20 gm. protein, 90 gm. fat, and 13 gm. carbohydrate, her urine became sugar-free on the third day and the ferric chlorid reaction was negative at the same time. Her diet was rapidly increased until she was receiving 55 gm. protein, 210 gm. fat and 34 gm. carbohydrate. At her body weight of 119 pounds, this represented 4 gm. fat per kilogram of body weight.

It will be noted from Chart 6 that her blood lipoids, which were slightly elevated at the initiation of treatment, fell promptly and remained only a little above normal.

Case 8 (21-3456).—An American housewife, 49 years of age, entered the hospital Nov. 30, 1921, with diabetes complicated by ulcers on the legs. Her family and past histories were without interest. She had noticed her increased thirst and polyuria about eighteen months before, soon after her husband, whom she attended, died of carcinoma of the face. Her symptoms had developed insidiously, and during the two years before admission her weight had fallen

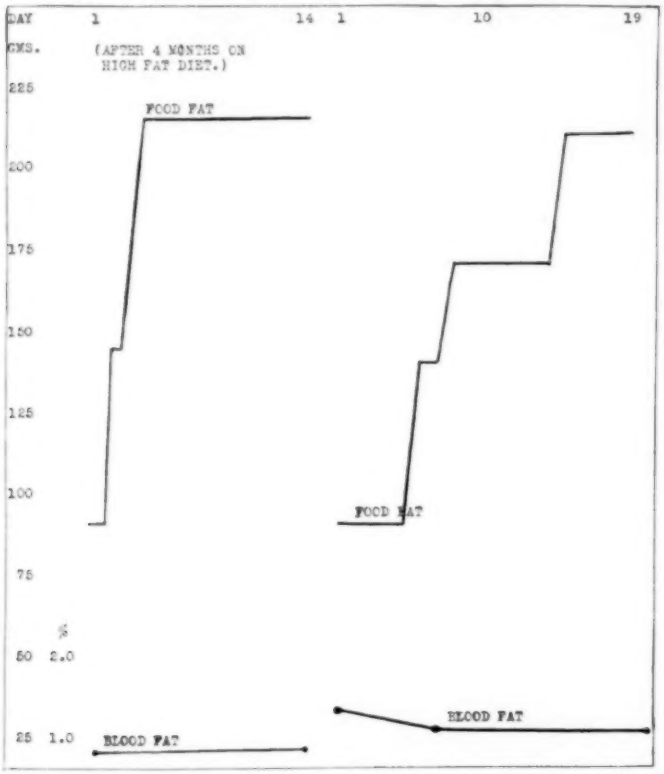

Chart 6.—Graphic chart from Cases 6 and 7.

from 165 to 101 pounds. The ulcers on her legs had developed during the last two months. There was a moderate degree of constipation, and her vision had been failing for two years. On physical examination there was evidence of a moderate degree of arteriosclerosis and cardiac enlargement. The knee jerks were markedly diminished and the Achilles reflexes could not be obtained. On the anterior upper third of the left leg were three ulcers resembling very much in appearance gummous ulcers.

On a diet containing 20 gm. protein, 85 gm. fat and 13 gm. carbohydrate her urine became sugar-free on the sixteenth day and the ferric chlorid reaction

was negative the next day. Her diet was increased until she was receiving protein, 55 gm.; fat, 200 gm., and carbohydrate, 33 gm. At a body weight of 103 pounds this represented 4.2 gm. fat per kilogram of body weight. It will be seen from Chart 7 that her blood lipoids were not elevated at any time.

CASE 9 (22-36).—An American farmer, 58 years of age, entered the hospital Jan. 16, 1922, complaining of the usual diabetic symptoms. There was no familial history of diabetes, and his past history was unimportant. The symptoms had appeared abruptly two years before, and urine examination at this time revealed the presence of glucose. Treatment by the "Allen method"

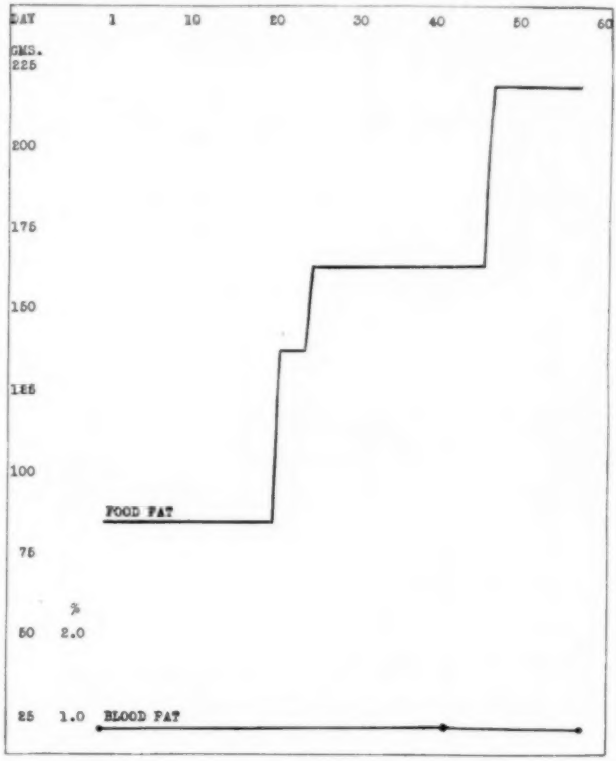

Chart 7.—Graphic chart from Case 8.

had been instituted on several occasions, but because of weakness the patient refused to adhere to the rigid regimen for more than thirty days at a time. In addition to the polyuria, polydipsia, and weakness, he complained of cramps in his legs, tingling of the feet, loss of weight from 140 to 102 pounds, failing vision, constipation, precordial pains and cardiac palpitation. Physical examination demonstrated slight cardiac enlargement and moderate arteriosclerosis; the knee-jerks were diminished and the Achilles reflexes could not be obtained. His urine, with a specific gravity of 1.046, contained a trace of albumin, glucose and a moderately strong ferric chlorid reaction. The blood sugar was 0.63. In the first twenty-four hour specimen there were 53.5 gm. sugar.

On a diet containing protein, 18 gm.; fat, 85 gm.; carbohydrate, 13 gm., his urine became sugar-free on the fifth day. Part of his record is shown in Chart 8. With a body weight of 110 pounds, his final diet allowed him 3.9 gm. fat per kilogram of body weight per day. Unfortunately, it was necessary for him to leave the hospital at the time indicated by the ending of the record. It will be seen, however, that the percentage of blood lipoids, which was at an approximately normal level at admission, was not increased by the administration of a diet deriving most of its energy from fat.

CASE 10 (22-610).—A 3 year old boy, American, entered the hospital March 6, 1922, with diabetes which had its onset in June, 1921, when the patient was 2 years of age. His father's brother had diabetes. The diagnosis was made

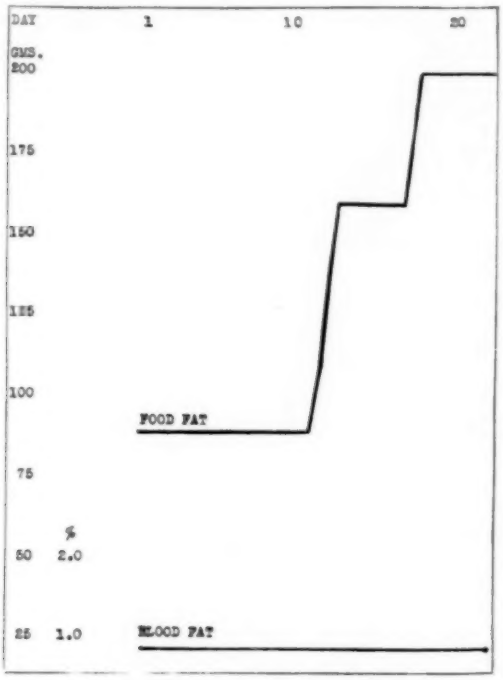

Chart 8.—Graphic chart from Case 9.

very soon after the onset of the symptoms, and rigorous dietetic treatment under the supervision of very competent physicians failed to control the glycosuria. During most of the period between the onset and his admission to the University Hospital, his diet contained about 40 gm. protein, 30 gm. fat, and 25 gm. carbohydrate, about 530 calories. His urine was sugar free at times during the first few weeks, but had not been at any time during the several months just previous to admission. His weight had fallen from 32 to 29 pounds. Examination was essentially negative. On a diet containing protein, 8 gm.; fat, 40 gm., and carbohydrate, 6 gm., he became sugar-free on the twelfth day. His diet was increased to include 15 gm. protein, 55 gm. fat and 10 gm. carbohydrate, without return of glycosuria. This allowed him 4.2 gm. fat per kilogram body weight. His blood lipoids, which were slightly high at first, had fallen to a normal level by the thirty-third day (Chart 9).

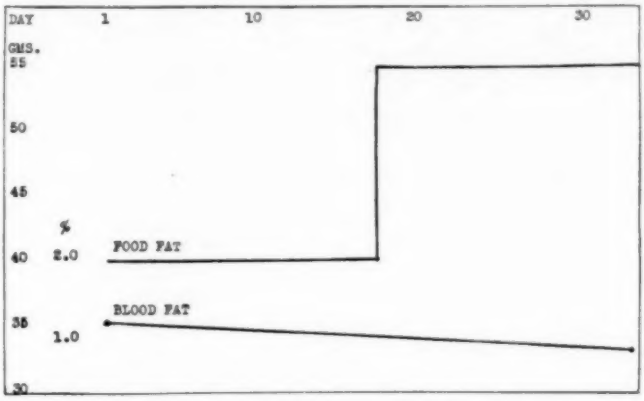

Chart 9.—Graphic chart from Case 10.

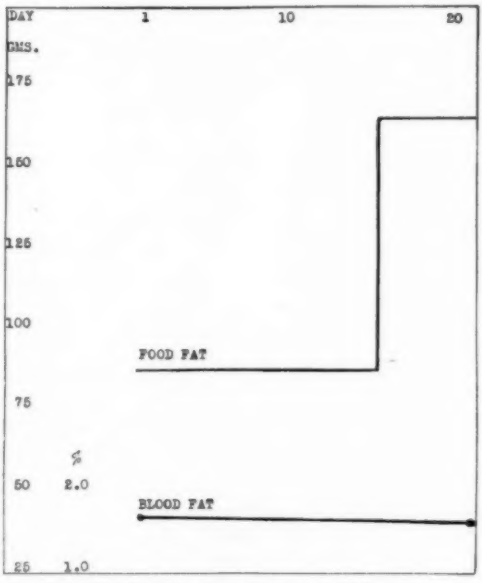

Chart 10.—Graphic chart from Case 11.

Case 11 (20-1021).—An American farmer, 45 years of age, entered the hospital April 19, 1922, complaining of weakness and polyuria. His mother had died at 51 of diabetes mellitus. His past history was unimportant, except that after his mother's death he had frequent analyses made of his urine. In December, 1920, polyuria developed abruptly, and with this progressive weakness, with his weight falling from 155 to 135. His home physician stated that "even by withholding all carbohydrates" he had not been able to reduce the glucose content of the urine below from 3 to 6 per cent. For the past three years he had on excessive exertion had attacks of precordial pain which radiated to the left shoulder and were accompanied by shortness of breath. There was moderate cardiac enlargement and evidence of early arterial sclerosis. The urine contained sugar and gave a heavy reaction with ferric chlorid. The carbon dioxid combining power of the blood plasma (Van Slyke) was normal, and the blood sugar was 0.50 per cent.

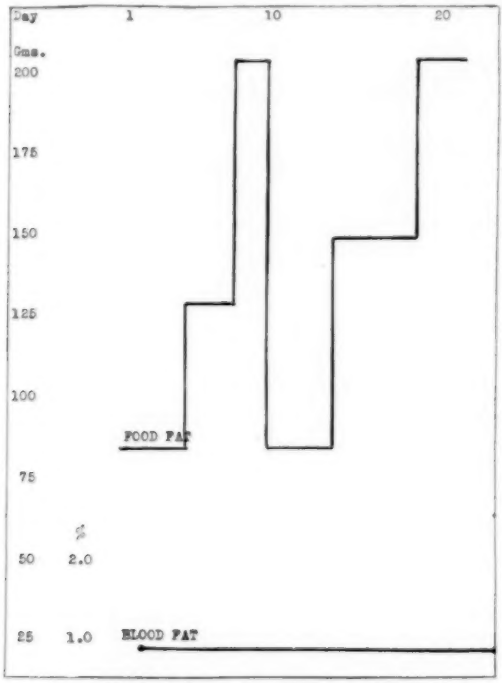

Chart 11.—Graphic chart from Case 12.

On a diet containing 18 gm. protein, 85 gm. fat, and 15 gm. carbohydrate his urine became sugar-free on the sixth day and the ferric chlorid reaction was negative a day later. Before our study of the case and the arrangement of his diet was completed he was called home by illness in the family, and further increases in his diet were made with the cooperation of his local physician. His blood lipoids, which were somewhat above normal at admission, did not fall during the brief period of observation, but neither did they rise (Chart 10).

CASE 12 (21-3573).—A retired merchant, 59 years of age entered the hospital, Dec. 9, 1921, with a mild diabetes of two years' duration. Previous treatment had been negligible, and his weight had fallen from 175 to 145 pounds. There were no important complications. His glycosuria was irregular, and it was found that he was eating outside the hospital. After he was desugarized and his food allowance had been increased to about 200 calories a day, he broke diet, and he was started again at a lower level. The record of his ingested fat and blood lipoids is shown in Chart 1. The final diet allowed him was 3.1 gm. of fat per kilogram of body weight per day. In spite of dietary irregularities, there was no increase in the blood lipoids.

From an examination of the records of these patients it is apparent that there was no increase in the lipoid content of the blood during the periods of observation, and, of much greater significance, that in the patients in whom a hyperlipoidemia existed when they first came under observation, the total fat fell to approximately normal levels. This is in accord with the observations of Blatherwick [9] in three cases of mild diabetes. It is certainly very strong evidence that the prevalent assumption which postulates that diabetic hyperlipoidemia is dependant on the excessive ingestion of fat is unwarranted. The explanation of this phenomenon must be sought in some other unusual feature of the diabetic state.

9. Blatherwick, N. R.: Observations on Blood Fat in Diabetes, J. Biol. Chem. **49**:193, 1921.

DEFECTS IN THE MEMBRANOUS BONES, DIABETES INSIPIDUS, AND EXOPTHALMUS, WITH REPORT OF A CASE

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The purpose of this paper is to report another case of defects in the membranous bones, diabetes insipidus, and exophthalmus, the seventh now in the literature, and to discuss some of the factors bearing on this disease.

REPORT OF CASE

History.—A girl, aged 7 years, first came under observation June 27, 1919. Her parents were well; there were one older and two younger children, and no miscarriages. Patient was a full term baby, normal in the first year. In the second year she was weak and did not develop as did the other children, since when she has been underweight and underheight. At 6 years a tooth became infected, followed without pain by a discharge from the left ear, and an infection of the left mastoid, which was opened and drained in October, 1918. Following this, her mouth became very sore with a bullous eruption on the gums, necessitating the removal of some of the unerupted permanent teeth.

A month after leaving the hospital, i. e., seven weeks after the mastoid operation, she suddenly developed a marked thirst and polyuria, so that in a few days she was taking as much as four quarts of water during the night and was passing about one and one-half gallons of urine in twenty-four hours.

Physical Examination.—Her weight was 30 pounds; height, 3 feet 8 inches. Skin very dry. Teeth and gums in bad condition; some of the permanent teeth have not appeared. A soft spot, oval in shape, measuring about 5x10 cm. can be felt in the right temporal bone. It has a well defined sharp, bony edge; it is not tender to slight pressure. Otherwise the skeleton seems normal. Exophthalmus of left eye. Heart, lungs, abdomen, and reflexes are all normal.

Urine: Very light color; specific gravity, 1.002; twenty-four hour amount about five liters; otherwise negative. Wassermann negative. Roentgenogram shows normal sella turcica.

Clinical Course.—The patient was lost sight of until Oct. 13, 1921, her tenth year. It was noticed that her mouth improved after cutting down sugar and starch intake as she had been advised to do, and that the soreness of the gums returned as soon as sugar was taken. She felt well and acted like other children, except for the thirst and polyuria, and was considered bright in school, where she was, however, only in the second grade.

Her weight was now 36 pounds, height 3 feet 8½ inches. The left ear was still discharging slightly. No obesity; genitalia normal for her age.

Eye examination showed a definite left exophthalmus; no increase in the intraocular pressure; fields of vision normal; color sense normal.

The blood showed white cells, 8,000; stained spreads normal, and blood sugar 0.10 per cent.

Urinary Findings.—A glucose tolerance test gave the result shown in Table 1. Only 15 gm. glucose were given instead of the usual amount, and even this made her gums very sore. It will be noted that the blood sugar was not abnormally increased by this amount. The amount of urine was not increased nor did sugar appear in it.

Urine collected according to the method of Mosenthal gave the results shown in Table 2, a reaction typical of diabetes insipidus. There is simply a large increase in the water excretion, with a consequent lowering of the

specific gravity. Although the night urine is enormously increased, its relation to the day urine is normal. Chlorids and nitrogen are excreted at a low concentration, but the total output is within normal limits.

On another occasion urine was again collected in the same way but 2.5 gm. sodium chlorid were given at 10 a. m. The result in Table 3 shows that chlorids are promptly and readily excreted, and that it is not necessary for this patient to increase the quantity of urine to get rid of this amount of chlorids.

TABLE 1.—GLUCOSE TOLERANCE TEST

Time	Blood Sugar, per Cent.	Urine		
		Amount, C.c.	Specific Gravity	Sugar
8:50	0.114	500	1.001	0
9:00 (15 gm. glucose)				
9:30	0.150	25	1.001	0
10:30	0.180	400	1.001	0

TABLE 2.—RESULTS FROM EXAMINATION OF URINE COLLECTED ACCORDING TO MOSENTHAL'S METHOD

Time	Amount, C.c.	Specific Gravity	Chlorids		Total Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8-10 a.m.	165	1.005	....	....	....	....
10-12 m.	220	1.006	....	....	....	....
12- 2 p.m.	355	1.002	....	....	....	....
2- 4 p.m.	330	1.003	....	....	....	....
4- 6 p.m.	370	1.004	....	....	....	....
6- 8 p.m.	730	1.004	....	....	....	....
Total day	2,170	.....	0.09	1.95	0.18	3.91
Total night	1,105	.....	0.05	0.55	0.16	1.77
Total 24 hours	3,275	.....	....	2.50	....	5.68

All specimens negative for albumin and sugar.

TABLE 3.—CHLORID EXCRETION

Time	Urine		Chlorid	
	Amount, C.c.	Specific Gravity	Per Cent.	Gm.
10 a.m.	325	1.001	0.13	0.42
Sodium chlorid 2.5 gm.				
12 m.	700	1.001	0.14	0.98
2 p.m.	600	1.007	0.47	2.82
4 p.m.	575	1.002	0.08	0.46
7 p.m.	650	1.000	0.07	0.46
10 p.m.	800	1.002	0.14	1.16
Total day	3,710	.....	....	6.30
Total night	1,800	1.004	0.14	2.52
Total 24 hours	5,510	.....	....	8.82

Roentgen-Ray Examination.—Roentgen-ray examination of the entire skeleton showed striking changes in the membranous bones. Large areas of the bones of the skull are rarified or completely absorbed leaving areas with well defined, scalloped edges where there is apparently no bone at all. These areas vary in size. The largest is about 10x5 cm. in the right temporal bone. They are scattered all over the skull including the bones of the orbit. It is of some significance to note that the bones forming the bridge of the nose are not involved, nor is the sella turcica, which is normal. A similar area is present in the lateral border of the left ilium where there is a semicircular defect about

6 cm. in diameter extending from the anterior superior spine to the acetabulum. Here, as in the cranial defects, there is complete absence of lime salts. There is deformity of the lower jaw with abnormal position of the teeth and apical infection of some teeth. The long bones, the vertebrae the carpal and tarsal bones, etc., are nowhere involved.

The changes noted are quite different from the changes found in syphilis, tuberculosis, osteitis fibrosa, Paget's disease, bone cysts, or sarcoma. In the complete absence of lime salts these lesions suggest

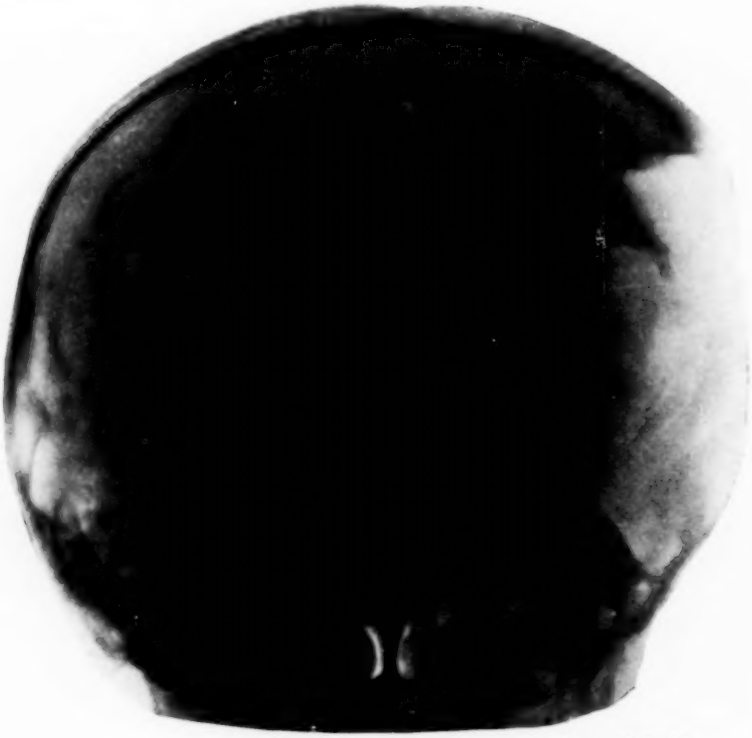

Fig. 1.—Front view of skull, showing extensive bony defects.

the changes found in some cases of bone metastases of carcinoma, and with this exception no difficulty should arise in making a differential diagnosis.

Effect of Pituitary Extract.—Oct. 19, 1921, pituitary extract, hypodermically, was administered; at first 1 c.c. once a day, later 0.5 c.c. twice a day, and was continued, with only an occasional intermission, for the next three months. At first the usual striking response was obtained. The urine decreased to 1,600 c.c. October 21; 1,400 c.c. October 22; 1,900 c.c. October 29. On days when no pituitary extract was given the output increased to 3 300 c.c.,

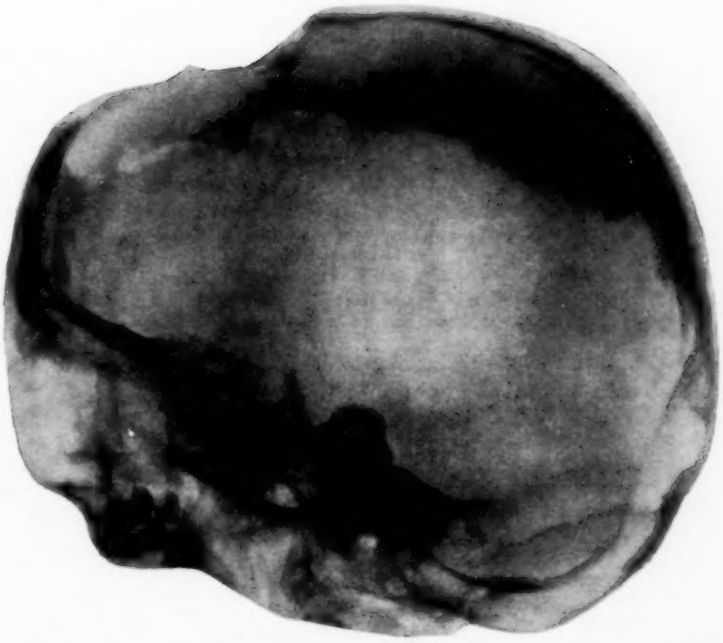

Fig. 2.—Side view of skull, showing extensive defects with normal sella turcica.

Fig. 3.—Pelvis with large defect in left innominate bone.

3,400 c.c., 4,300 c.c., etc. November 11, however, even with 0.5 c.c. pituitary extract twice in the day, the patient excreted 5,700 c.c. urine, and from then to Jan. 6, 1922, the output never went down very strikingly. The amounts measured ranged from 2,000 to 5,000 c.c. in addition to which specimens were lost every night. It is true that on days when no pituitary extract was given the amount went to 6,000 c.c., but it seemed obvious that the patient was not responding to pituitary extract in a satisfactory manner. January 6, she developed great weakness, substernal pain, dyspnea and nausea, symptoms apparently due to the pituitary extract, and since then no injections have been given.

March 11, 1922, she had been passing from 3,000 to 6,000 c.c. urine per day. She was now 10 years old. Her weight was 39 pounds, the average for a girl of 5 years; her height was 3 feet 9 inches, the average for a girl of 7 years. There was no apparent change in the bony defects of the skull.

Here, then, was a girl showing dwarfism, diabetes insipidus, defects in the membranous bones, and unilateral exophthalmus.

DISCUSSION

It is not our purpose again to review the literature on this subject, which has been done admirably by Christian [1] and also by Hand.[2] A

TABLE 4.—REPORTED CASES

Case Reported by	Sex	Age	Bone Defects	Polyuria	Sella	Exophthalmos
Hand [2]	M	3	+	+	No X ray	+
Hand (Key) [2]	M	7	+	+	No X ray	+
Hand (Luburg) [2]	M	4	+	+	Normal	+
Christian [1]	M	5	+	+	Defect	+
Schüller [3]	M	16	+	0	Normal	+
Schüller [3]	F	4½	+	+	Defect	+
Author	F	10	+	+	Normal	+

careful search failed to reveal any new cases. For reference the six cases already reported and the one here reported are outlined in Table 4.

Slight similarity is found in a series of ten cases reported by Barber,[4] under the title "Renal Dwarfism." These are cases characterized by the development from the tenth to the seventeenth year of typical rachitis with chronic interstitial nephritis and, in eight of the ten cases, marked increase of thirst, all of the patients exhibiting some degree of dwarfism. The bone defects did not, however, involve the membranous bones, exophthalmus was not present in any of the cases, nor was the polyuria as striking as in this series, and they are therefore omitted.

1. Christian, H. A.: Defects in Membranous Bones, Exophthalmus, and Diabetes Insipidus. Contribution to Medical and Biological Research. Paul B. Hoeber, New York **1**:390, 1919.

2. Hand, A.: Defects of Membranous Bones, Exophthalmus and Polyuria in Childhood, Am. J. M. Sc. **162**:509, 1921.

3. Schüller, A.: Ueber eigentartige Schädeldefekte in Jugendalter, Fortschr. a. d. Geb. d. Roentgenstrahlen, **23**:12, 1915.

4. Barber, H.: Renal Dwarfism, Quart. J. M. **14**:55, 1921.

In the seven cases here tabulated the constancy of defects of the membranous bones, of polyuria and of exophthalmus is so evident that one seems justified in grouping them together. No new theories are advanced here to account for the condition, but it seems pertinent to call attention to certain observations that have already been made. One is tempted at first to attribute the condition somehow to disease of the hypophysis, because the hypophysis is thought to exercise control over the growth of the skeleton and because it is so firmly regarded as the seat of the trouble in diabetes insipidus. Indeed, the exploitation of the hypophysis advanced to such a state that it became necessary recently for Cushing [5] to file new credentials for it in no uncertain terms. About the only evidence that diabetes insipidus originates in the hypophysis is that pituitary extract temporarily relieves the polyuria and that polyuria occasionally follows hypophyseal operations. Evidence like the first, so often advanced, is, of course, entirely unreliable. The fact that a drug relieves a symptom is no sign that the symptom is due to a deficiency of the drug. One wonders why the suprarenals have not been more often blamed for asthma because epinephrin relieves the paroxysms. Moreover, the polyuria following hypophyseal operations is too inconstant to be of much value. We have very little evidence that pituitary extract is discharged into the circulation at all. It seems probable that it is a product of glia cells of nothing more than pharmacologic interest.

The work of Bailey and Bremer [6] is of especial importance in this connection. They have shown that whereas polyuria following experimental lesions of the hypophysis is usually temporary, lesions of the hypothalamus may produce a permanent polyuria and polydipsia, sometimes even associated with adiposogenital dystrophy. These conditions can be produced after the temporary polyuria following hypophyseal operations has subsided. This polyuria from lesions of the hypothalamus has apparently all of the characteristics of diabetes insipidus in man. It seems probable that tumors of the hypophysis produce diabetes insipidus in man only when they press upward on the brain stem, thereby involving centers in the hypothalamus, the tuber cinereum, or the floor of the fourth ventricle.

In considering diabetes insipidus it is important to keep three factors in mind. First, is the factor in the central nervous system already referred to; second, the functional capacity of the kidney must

5. Cushing, H.: Disorders of the Pituitary Gland, J. A. M. A. **76**:1721 (June 18) 1921.

6. Bremer, F., and Bailey, P.: Experimental Diabetes Insipidus and Genital Atrophy, Endocrinology **5**:761, 1921. Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921.

be considered, and third the maintenance of the water balance of the body. There is little evidence to show that the kidney function is impaired; much to show that it is not impaired. Nitrogen products and chlorids in the blood are maintained at a normal level as long as the patient may take all the water that he desires. When sodium chlorid is administered, it is excreted quickly, sometimes at such a high concentration that increased diuresis does not occur. If water is withheld, the rise in blood chlorids is very great, sometimes even reaching 1.03 per cent.,[7] but at times the power of salt concentration is retained as high as three fold.[8]

Veil [9] investigated most thoroughly the chlorid factor in these cases. He concludes that there are two forms of diabetes insipidus, the one showing hyperchloremia after the ingestion of sodium chlorid, the other hypochloremia. He shows that puncture of the midbrain produces polyuria of the first type, i. e., hyperchloremia with hypochloruria; while puncture of the fourth ventricle produces polyuria of the second type, i. e., hypochloremia with hyperchloruria. This again complicates the rôle of the hypophysis in diabetes insipidus.

The water balance of the body is regulated both by the satisfaction of thirst and by the excretion of water by the kidneys. These are to some extent independent functions. Polyuria may occur without any increase in water intake as it does when patients with diabetes insipidus for any reason go into coma, while excessive thirst may occur without any great loss of fluid from the body. It is the function of the kidney in all animals that have kidneys to keep the osmotic pressure of the blood at the primordial pressure of sea water. If water is ingested by a healthy person, diuresis quickly occurs; if salt is taken, thirst is promptly felt. The cause of the sensation of thirst is still unknown. Cannon's attractive theory of irritation of the nerve endings in the throat seems entirely refuted by the work of Wier, Larson, and Rowntree [10] who showed that anesthetizing the throat has no effect on thirst. If more water is taken than can be excreted promptly, it is probably stored in the cells of the tissues. For Cohnheim showed that animals could be given physiologic solution of sodium chlorid to the extent of 90 per cent. of their body weight without the development of edema. Incidentally, it was found later that it is necessary to inject the fluid intermittently at about the rhythm of the heart. If injected in a

7. Socin, C.: Ueber Diabetes Insipidus, Ztschr. f. klin. Med. **78**:294, 1913.
8. Goldberg and Herz: Rev. de méd. **33**:310, 1913.
9. Veil, W. H.: Intermediare Vorgänge bei Diabetes Insipidus, Biochem. Ztschr. **91**:317, 1918.
10. Wier, Larson, and Rowntree: Studies in Diabetes Insipidus, Water Balance, and Water Intoxication, Arch. Int. Med. **29**:306 (March) 1922.

continuous stream, edema does occur; and if the secretion of urine is in any way impaired, toxic symptoms occur, among them headache, vomiting, dyspnea, cramps, twitching, ataxia and convulsions. In diabetes insipidus, even with the large intake and the large output, the water balance is ordinarily well maintained. As in normal persons, we have very little evidence of a nervous control of the kidneys.

Returning to the case reported, the relation of the polyuria to the bone defects is puzzling. Embryologically, the pituitary bears a relation to the membranous bones of the skull. In the lower vertebrates, such as the amphioxus, the vertebral column is composed of the notochord. In the human the notochord, which has become the intervertebral discs, ends at the sella turcica. From here the axial portion of the skeleton is continued forward to form the base of the occipital bone and the body of the sphenoid, both of which are formed from cartilaginous bone. The other bones of the cranium are, however, formed in the mesenchyme of the head, where ossification takes place directly into tissue like the connective tissue of the skin. Embryologically, then, the sella turcica and the membranous bones of the skull lie just anterior to the end of the axial skeleton.

The rôle of infection in the etiology of diabetes insipidus deserves more consideration than it receives in the literature. In this case it will be noted that the onset of the polyuria occurred a few weeks after an operation on an infected mastoid. In one other case of the series there was an infected ear and in the case reports of two other patients sore mouths and bad teeth are mentioned. Two other cases of polyuria are known, neither yet reported in the literature, both of which were associated with mastoid disease. In one case the polyuria persisted for a week after operation, until a subdural abscess evacuated itself through the mastoid incision. The other case also followed an operation on an infected mastoid. What part the infection played and what part pressure on and injury to the base of the brain played is, of course, impossible to say, but it will be of interest to know what the incidence of infection in the mastoid, the ear, and the mouth is in polyurias of the diabetes insipidus type.

CONCLUSIONS

1. A case is reported exhibiting some degree of dwarfism, diabetes insipidus, defects in the membranous bones of the skull and pelvis, and exophthalmus.

2. Pituitary extract hypodermically controlled the polyuria temporarily. After a time the effect of pituitary extract diminished. It had no effect on the bone defects.

3. The etiology of this disease is unknown.

4. Diabetes insipidus is not a disease entity, but more likely a clinical syndrome of disease of the base of the brain caused by pressure, injury, or infection.

We wish to thank Mr. H. W. Dachtler, of Toledo, for his careful roentgenologic studies of this patient.

ORTHOPNEA *

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Numerous theories have been advanced from time to time to account for orthopnea, but there has been surprisingly little discussion of the subject. Hewlett [1] sums it up as follows:

> It is well known that patients suffering from dyspnea, and particularly those suffering from cardiac dyspnea, cannot breathe as comfortably when lying down as when sitting up. The dyspnea which necessitates an upright posture is spoken of as orthopnea. The exact cause of orthopnea is not definitely understood. According to the views of earlier authors, the sitting posture allows better fixation of the shoulders, and this favors the use of the accessory muscles of inspiration, but Hofbauer showed that these patients experienced their chief difficulty in expiration rather than inspiration. The upright posture is a more favorable one for expiration, because the anterior abdominal wall is pushed out by the lower position of the abdominal viscera, and when it contracts during forced expiration it works at a better mechanical advantage. In the sitting posture, also, the diaphragm takes a lower position. As a result of this, the thoracic cavity is enlarged and the size of the lungs is increased. It seems probable that this pulmonary distention assists the pulmonary circulation by increasing the caliber of the pulmonary capillaries. Finally, a high position of the diaphragm may lessen the aperture traversed by the inferior vena cava, and it may thus obstruct the return flow of blood from the lower parts of the body. A lower position of the diaphragm, such as occurs in the sitting position, would remove this obstruction. It is difficult, at the present time, to say which of these possible advantages is the most important in contributing to the relief which dyspneic cardiac patients frequently experience in the sitting posture.

The thought occurred to one of us (C. D. C.) that orthopnea might be dependent on an excessive reduction in the vital capacity of certain patients when they lie down. On searching through the literature to learn the normal percentage of reduction, few observations were found on this particular phase of the subject of vital capacity, and the standards of comparison did not seem satisfactory. Furthermore, several observations which we made at random on persons about the laboratory, tended to refute the flat statement that the vital capacity is always smaller in the lying posture. Consequently, it was decided to check the subject on a large series of normal subjects. The results have been recorded in a previous communication.[2]

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1. Hewlett: Monographic Medicine **1**:375.
2. Christie and Beams: Arch. Int. Med. **30**:34 (July) 1922.

We found from this series of observations on 290 normal men and women, between the ages of 20 and 30, that there is 5.5 per cent. less vital capacity in the lying than in the sitting posture for all groups when averaged; that approximately 80 per cent. of all normal persons have a smaller vital capacity lying than sitting; and that with rather obese normal women this difference may amount to as much as 20 per cent. We further found that nearly 20 per cent. of the normals of our series have a vital capacity which is practically the same when they recline as when they sit. Some persons can even expire more lying down than sitting, and in two instances of big healthy and intelligent medical students we found that they had nearly 10 per cent. more vital capacity lying down than sitting. We did not observe any differences in type of chest which seemed to account for these disparities. We concluded further from these observations that normal persons of the same sex and same body surface have surprisingly near the same vital capacity; in fact, those with variations constitute only about 10 per cent. It was shown also that as the body surface increases, there is a fairly constant increase in the vital capacity; that is to say, a normal female between 20 and 30 years of age, with a body surface of from 1.4 to 1.5 square meter, has a vital capacity of 2,700 c.c., and with each increase of 0.1 square meter the vital capacity goes up 125 c.c. With normal males between 20 and 30 years of age, with a body surface of from 1.6 to 1.7 square meter, there is an increase of 350 c.c. in the vital capacity for each additional 0.1 square meter added to the body surface. When these results were all totaled, it was found that normal females between the ages of 20 and 30 years have a vital capacity of 1,970 c.c. for each square meter of body surface; and healthy males of the same ages have a vital capacity of 2,470 c.c. for each square meter of body surface. These results agree closely with those published by West.[3] Given, then, a patient with a reduction in vital capacity, these latter figures allow us to estimate fairly accurately the normal vital capacity that persons should have. It is only necessary to know the body surface, and if the patient be a female multiply the estimated body surface by 2,000 c.c., and if a male multiply the estimated body surface by 2,500 c.c.

It is our belief that there will not be genuine orthopnea without a great reduction of the vital capacity, the most common cause of which is cardiac disease, although it may be reduced greatly as the result of other conditions, such as pulmonary tuberculosis (and, of course, the more advanced the greater the reduction), pleurisy with effusion, large lung or mediastinal tumors, bronchiolar spasm, and finally paresis of the external muscles of respiration, such as is seen in syringomyelia

3. West: Arch. Int. Med. **25**:306 (March) 1920.

and anterior poliomyelitis. It is possible, therefore, to have genuine orthopnea in any of the above mentioned conditions providing they encroach sufficiently on a healthy lung to cause a very severe reduction in the vital capacity.

A simple example will serve to bring out the point which we have in mind. Given a patient with severe cardiac disease, whose vital capacity when he sits erect has been reduced to 1,000 c.c.—if he has a body surface of 1.6 square meter, his normal—a vital capacity should be 4,000 c.c. (body surface × 2,500 c.c.). He has, therefore, only 25 per cent. of his vital capacity left, or a 75 per cent. reduction. This reduction is quite sufficient to use up any luxus which he had, and he is, therefore, down to the irreducible minimum in the sitting posture. What happens if this same patient lies down? There is an immediate reduction in his vital capacity by 5.5 per cent. of 4,000, that is, 220 c.c., which would be the normal difference between his sitting and lying postures. But when he already has a reduction of the vital capacity to 1,000 c.c., this 5.5 per cent. reduction or 220 c.c. becomes a 22 per cent. reduction, and he has in the supine position a remaining vital capacity of only 780 c.c., which is wholly inadequate for his needs. The whole luxus was used up in the first great reduction, and now if he lies down and incurs this additional encroachment it is immediately felt.

Orthopnea is commonly seen in severe cardiac disease, so commonly, in fact, that the condition has almost come to be looked on as something peculiar to and coincident with severe heart lesions. It is quite obvious, of course, that such is not the case, for there is a great variety of clinical conditions which will give the proper stage settings, as it were, for typical orthopnea, quite as genuine and characteristic as is ever encountered in severe cardiac disease. The idea that orthopnea must be associated with severe cardiac lesions has been responsible, we believe, for the suppression of facts which shed considerable light on this symptom.

That several important factors are to be taken into consideration as probable causative agents in the production of orthopnea is apparent. It is our conviction, however, that reduction in vital capacity is the primary factor. Without a severe reduction the condition cannot exist, and the more extreme the reduction the more likely the condition is to appear. Contributory or associated conditions which increase the severity of orthopnea are moisture in the lungs and painful inflammation of the pleura, both of which stimulate the cough reflex and thereby cause increased work on the part of the organism, with consequent increase in metabolism and the necessity for increased ventilation on the part of lungs already sorely embarrassed from the great reduction in the vital capacity. It becomes apparent, then, that any other factors causing

an increase in the metabolic rate and, therefore, demanding increased pulmonary ventilation would be contributory causes, as fever, restlessness, or exercise.

With these fundamental considerations, we believe it is quite apparent that orthopnea may be present in any condition which gives rise to severe reduction in the vital capacity of the lungs, with the liklihood of its being still greater if any of the contributory causes are present. It is not strange or peculiar, then, that it should be so often and so commonly seen in cardiac diseases, for in this condition we constantly find a reduction of the vital capacity, and the more severe the embarrassment of the heart, the greater the reduction of the vital capacity. This has long been known, but the admirable work of Peabody during recent years has emphasized the fact and greatly amplified our knowledge of the subject.

We believe that orthopnea may be subdivided into (1) orthopnea of choice, and (2) orthopnea of necessity. In reality, the two conditions are precisely the the same, the only difference being one of degree. "Orthopnea of choice" is by far the more common. In this condition the patients prefer to sit up, but it is not essential to their well being for they can lie down and remain comfortable. In fact, we have made observations on these patients with regard to their breathing, and find that they are practically just as well off lying down as sitting. There is no apparent increase in their respiratory rate or volume and no increase in the pulse rate. From closely questioning many of them we have come to the belief that much of the "orthopnea of choice" is simply a matter of the patient's being just a bit easier in the upright position. That is to say, when he lies down and the additional 5.5 per cent. of his normal vital capacity is taken away, he notices it and becomes apprehensive. This is particularly true if he becomes restless in bed and thereby increases his metabolism, which, in turn, causes a demand for increased respiration from a vital capacity that is much reduced.

"Orthopnea of necessity" is, as the name implies, a condition which the patient brings about for self-preservation. These cases are in the minority but they are not uncommon. The patients assume the upright posture to take advantage of every available cubic centimeter of vital capacity. We believe them to be persons who normally have a considerably smaller vital capacity in the lying than in the sitting posture; but with many of them one does not have to assume a bigger reduction than the average of 5.5 per cent. to explain their discomfort. Take as an example, a person like the one discussed previously, whose normal vital capacity of 4,000 c.c. has been reduced by disease to 1,000 c.c. If he should lie down there would be a further reduction to 780 c.c., which

would, of course, be wholly inadequate. Add to that a fever or an exhausting cough, both of which would increase the metabolic rate or the demand for greater pulmonary ventilation, and it is easy to see that this patient could not survive for a very long time. If the patient for any reason lies down in bed, there is an immediate struggle on his part to get up. His respiratory rate goes up, if it is possible; there is acceleration of the pulse rate, cyanosis increases, and the patient becomes greatly alarmed, struggles frantically for air, and looks with intense horror on what appears to him as impending disaster. This is the picture in our minds of "orthopnea of necessity."

It is obvious, then, that orthopnea is largely a question of vital capacity. If there is for any reason just about sufficient reduction to use up the luxus, the additional loss of 5.5 per cent. of the original normal vital capacity on assuming the lying position is immediately felt by the patient, and he prefers sitting up to preserve even so small an amount, for then he is not quite so much aware of his respiratory needs. But in another case, if the luxus is entirely used up when the patient is in the sitting posture so that respiration is already increased, and he is now for any purpose put in a supine position, the additional loss of 5.5 per cent. of vital capacity becomes unbearable, and unless it is immediately restored disaster will follow.

It is not uncommon to see two patients with cardiac lesions equally severe only one of whom has orthopnea. From all external evidences, the patients should be afflicted equally, but such is not the case. This has mystified us many times, but we think the explanation is simple. They may have their vital capacity reduced to the same degree, but the one who has orthopnea falls among the 80 per cent. who suffer a varying degree of reduction on lying down, while the other comes in the smaller group of those who have practically the same or even a greater vital capacity when lying down. We have repeatedly had confirmation of this fact. For instance, one orthopneic patient with his vital capacity reduced to 1,200 c.c. has, when he lies down, a vital capacity of, say, 950 c.c. This patient is one of the great 80 per cent. group of those who get a reduction of their vital capacity when they lie down. Another patient with just as severe a cardiac lesion has no particular orthopnea though his vital capacity also is reduced to 1,200 c.c. When this patient lies down it will be found that his vital capacity is still 1,200 c.c. or may be even 1,400 c.c., so that there is obviously no need for him to sit, as he is quite as comfortable lying down as sitting.

There are all degrees of this condition, but it seems obvious to us that "orthopnea of choice" and "orthopnea of necessity" are two clearly defined symptoms and their recognition is a simple procedure. We further believe that the establishment of the fact that perhaps 20 per

cent. of people breathe as much, if not more, when lying down is the final answer to the mystifying question of why some patients with severe cardiac disease do not have orthopnea.

DISCUSSION

When this work was first under consideration, we were sceptical of our ability to get the maximum expiratory effort when a patient with intense orthopnea was reclining. We have, in fact, had failures owing to our inability to gain the cooperation of the patient, but we have four chief reasons for thinking that the results herein recorded are as nearly accurate as can be obtained under the conditions: (1) Repeated attempts were made, and in each instance the maximum that the patient breathed sitting or lying was the value chosen. (2) Our forty-two patients with reduced vital capacity from disease lost only 5.9 per cent. of their estimated vital capacity when lying down, while our 290 normal subjects lost 5.5 per cent. of their vital capacity when lying down. (3) Approximately 80 per cent. of our 290 normal had under the same conditions within 50 c.c. of their sitting vital capacity or even more; while of our patients with vital capacity reduced from disease, 81.5 per cent. expired less lying down and 18.5 per cent. came within 50 c.c. or breathed more lying down than sitting. (4) There is only one patient in the series (J. W., Table 1) who lost more than 10 per cent. of his estimated normal vital capacity on lying down. He was our worst case of "orthopnea of necessity," but we had among our normal males those who lost as much as 10 per cent. on lying down, and in the case of the females, two of them who were obese showed a loss of 20 per cent. of their vital capacity in the supine position. So it may be that J. W. in health would have reacted as did these normal subjects. However, in the face of evidence to the contrary, it is quite likely that the acute distress of most of the patients in this group did vitiate our results to a certain extent, for if we take only the group of cases with "orthopnea of necessity," we find that they lose on lying down 8 per cent. of their estimated normal vital capacity, which may indicate that they lost a little more as a result of their disease. However, to establish the validity of our claims, we do not need such a great percentage of loss due to posture as 26.5 per cent., or one-fourth of the remaining vital capacity, which is the average reduction for all patients in this group.

We must add that all of the patients with "orthopnea of necessity" tabulated in Table 1 had some of the contributing causes of orthopnea, such as fever, cough, pain, nervousness, all of which would increase metabolism and thereby create a greater demand for pulmonary ventilation from a greatly inadequate ventilating surface.

It should be noted also that all of these patients in Table 1 breathed less lying down than sitting, and we believe most of them when in health would have responded like the 80 per cent. of normals.

All of the figures in Table 1 were totaled in our averages, except those in the last two observations on M. T., which were made after he had improved.

The cases of "orthopnea of choice," as tabulated in Table 2, were very similar to those in Table 1, the difference being largely one of degree. They could lie down and remain fairly comfortable, but they preferred to sit upright. Many of these patients had doubtless had "orthopnea of necessity," but were better when we saw them as the result of rest or therapy. All of them lost an additional amount of their vital capacity on lying down, with the exception of one (T. S.). She said she was more short of breath lying down, but it is to be doubted, because she showed no increase in pulse rate or respiratory rate after lying down twenty minutes. She was very nervous and apprehensive and died subsequently.

Doubtless some of these patients cited in Table 2 would have had "orthopnea of necessity" had there been any contributory cause, such as increase in metabolism. But clinically they were not so acutely distressed as were those in Table 1. One patient (N) nicely illustrates this point. While she had a gross reduction of her vital capacity from pleural effusion (massive) and cardiorenal and vascular disease, yet she was free from any of the exciting causes of an increase in metabolism. She sat up in bed day after day without an ache or pain, and breathed in apparent comfort.

Table 3 shows a group of patients with varying degrees of reduction in their vital capacities but with no orthopnea. It will be noted that (except three patients who will be discussed later) none of them showed the extensive reductions from disease that were tabulated in the two other tables, nor did they show a great percentile loss of vital capacity due to lying down. In fact, with the exception of one case this group contained all of the 18.5 per cent. who showed no change or a gain in vital capacity on lying down.

The second patient in Table 3 (A. J.) was a man with extreme loss of vital capacity due to very marked cardiac decompensation, as severe, in fact, as in many of the cases with "orthopnea of necessity." This patient, it will be noted, was not orthopneic, and could and did lie down perfectly well. It was proved that his vital capacity was decidedly greater lying than sitting. This man, we believe, belongs to the 20 per cent. group of our normal individuals who breathe as much or more when lying.

The results from the two observations made on Mrs. T. were not included in our totals, since we believe the upright vital capacity was

TABLE 1.—Analysis of Cases of Orthopnea of Necessity

Name	Age	Sex	B. S.	Estimated Vital Capacity Females, B. S. × 2,000 Males, B. S. × 2,500		Estimated Reduction Due to Posture 5.5 % of Sitting Vital Capacity	Actual Vital Capacity as Result of the Disease		Per Cent. of Reduction from Normal	Difference Due to Posture	Per Cent. of Reduction Due to Posture	Condition of Patient
				Sitting	Lying		Sitting	Lying				
M. J.	45	F	1.6	3,200	3,024	176	1,085	883	66	202	18.6	Decompensation; rales at bases; liver engorged; blood pressure 230/110; edema
L. P.	39	F	1.7	3,400	3,213	187	1,092	667	69	395	38	Edema; rales; tender liver; cough; double aortic; fever; endocarditis
T. S.	35	M	1.83	4,575	4,323	251	1,149	883	76	266	23	Evident decompensation; liver engorged; rales at bases
M. T.	55	M	1.6	3,690	3,487	202	1,213	883	58	330	28	Edema; branch block
			1.6	3,690	3,487	202	1,276	1,128	58	148	11	Prefers to sit up
			1.6	3,690	3,487	202	1,450	1,340	51	100	7.8	After therapy; can lie down; edema less
			These two determinations are not figured in the totals									
J. W.	26	M	2	5,000	4,725	275	1,107	567	78	540	48	Extreme decompensation; aortic insufficiency and stenosis
E. S.	43	F	1.6	3,200	3,024	176	1,107	905	66	202	18	Auricular fibrillation; decompensated chronic myocarditis
S. S.	56	M	1.95	4,388	4,146	242	1,318	1,107	70	211	16	Cyanosis; edema; liver engorged; rales
M. W.	35	M	1.9	4,750	4,488	261	1,800	1,400	62	400	22	Rales; cough; fever; aortic insufficiency and stenosis
F. C.	55	F	1.5	2,700	2,551	148	1,002	667	61	395	38	Myocarditis; bronchitis; fever

TABLE 2.—Analysis of Cases of Orthopnea of Choice

Name	Age	Sex	B. S.	Estimated Vital Capacity Females, B. S. × 2,000 Males, B. S. × 2,500		Estimated Reduction Due to Posture 5.5 % of Sitting Vital Capacity	Actual Vital Capacity as Result of the Disease		Per Cent. of Reduction from Normal	Difference Due to Posture	Per Cent. of Reduction Due to Posture	Condition of Patient
				Sitting	Lying		Sitting	Lying				
S. W.	43	F	1.7	3,400	3,213	187	1,758	1,537	49	221	12.6	Cardiovascular and renal; some edema; few rales at bases
N.	35	F	1.5	3,000	2,835	165	774	709	78	64	8.2	Pleural effusion, both chests; no moisture; no cough; cardiovascular and renal
			1.5	3,000	2,835	165	971	774	68	197	20	After withdrawing some fluid
E. S.	64	F	1.5	2,700	2,551	148	1,302	1,107	50	255	18	Liver tender; slight edema
M. C.	72	F	1.68	3,024	2,907	116	1,340	1,122	59	218	15.4	Some decompensation
J. P.	60	M	1.7	3,825	3,615	210	1,500	1,402	61	98	6.5	Luetic myocarditis; cerebral sclerosis; few signs
A. G.	50	M	1.77	3,983	3,764	219	1,550	1,250	60	300	19	Chronic myocarditis; edema; fluid, right pleural cavity
T. S.	44	F	1.8	3,600	3,402	198	1,626	1,626	55	0	0	Slight edema, etc.
G. S.	48	M	2.05	4,613	4,359	254	2,100	1,900	55	200	9.5	Endocarditis; auricular fibrillation; slight decompensation
G. M.	64	M	2.03	4,568	4,307	251	2,829	2,633	48	196	7	Edema; tender liver; rales at bases, etc.
E. S.	50	F	1.63	3,260	3,021	179	1,475	1,150	55	325	22	Fluid, right pleural cavity; edema
S.	45	M	1.9	4,750	4,488	261	2,306	2,010	52	296	12	No sign of decompensation
F. S.	45	M	1.8	4,500	4,252	247	2,130	1,974	53	156	7.3	Slight edema; gallop rhythm
J. B.	61	M	1.65	3,713	3,409	204	1,494	1,213	60	281	12	Moderate decompensation; metabolic rate, 11 per cent. above normal
F. P.	37	M	1.7	4,250	4,016	233	3,115	2,829	27	286	9.1	Mitral disease; no increase in respiratory rate; no signs of failure

F. P.	27	M	1.7	4,250	4,016	233	3,115	2,829	27	286	9.1	Mitral disease; no increase in respiratory rate; no signs of failure

TABLE 3.—Analysis of Cases with Reduction in Vital Capacity Without Orthopnea

Name	Age	Sex	B. S.	Estimated Vital Capacity Females, B. S. × 2,000 Males, B. S. × 2,500		Estimated Reduction Due to Posture 5.5 % of Sitting Vital Capacity	Actual Vital Capacity as Result of the Disease		Per Cent. of Reduction from Normal	Difference Due to Posture	Per Cent. of Reduction Due to Posture	Condition of Patient
				Sitting	Lying		Sitting	Lying				
W. K.	70	M	1.95	4,388	4,146	242	2,845	2,523	35	322	11	Chronic bronchitis; emphysema; left ventricle, hypertrophy
A. J.	49	M	1.8	4,050	3,827	223	1,171	1,318	72	+137	+11.6	Chronic myocarditis; decompensated; emphysema
M. B.	11	M	1.08	2,760	2,551	148	1,868	1,626	31	242	13	Congenital heart; cyanosis; no decompensation
M. M.	30	M	1.85	4,025	4,371	254	2,108	2,196	55	+88	+4	Aortic disease; liver tender; slight edema
B. H.	40	F	1.6	3,200	3,024	176	1,953	1,846	39	107	5.4	No evidence of decompensation
P. R.	45	M	1.58	3,950	3,732	217	1,911	2,086	52	+175	+9	Fibrillation; no edema
F. G.	45	M	1.57	3,925	3,715	210	3,938	3,757	0	181	4.6	Aneurysm of aorta
M. C.	44	M	1.62	4,050	3,827	223	2,750	2,750	32	0	0	Chronic bronchitis; emphysema; asthma
Mrs. T.	43(?)	F	1.5	3,000	2,835	165	905	1,340	70	+435	+48	Diminution in vital capacity due to syringomyelia; no rales, cough or fever
			1.5	3,000	2,835	165	883	1,192	71	+309	+35	Patient had no cause for increased metabolic rate; could do nothing but lie quiet
			(Neither this nor the above result enters into our totals)									
E. C.	23	F	1.54	3,080	2,911	160	1,700	1,650	45	50	3	Moderate dilatation of right auricle, aortic and mitral; acute rheumatic fever
S. M.	13	M	1.32	3,300	3,118	182	2,306	2 086	28	310	12	Hyperpnea; no particular orthopnea; acute endocarditis and nephritis
Mrs. B.	45	F	1.6	3,200	3,024	176	2,152	1,890	23	262	12	Mitral disease; fibrillation; no edema
C. M.	52	M	1.7	3,825	3,924	210	3,179	2,961	20	218	6.8	Slight edema; fibrillation
L. P.	43	M	1.71	4,275	4,039	235	3,543	3,328	18	215	6	No edema; no moisture at bases
S. M.	26	M	1.58	3,950	3,732	217	3,982	3,938	0	44	1	No edema; mitral disease, slight
J. V.	21	F	1.35	2,700	2,551	148	2,196	2,196	20	0	0	Endocarditis; no decompensation
J. W.	36	M	1.90	4,900	4,630	270	5,201	4,855	0	346	6.6	Complaint, heart trouble; no disease
A. R.	37	M	1.64	4,100	3,875	225	3,436	3,137	16	299	8.7	Endocarditis; no signs of failure
S. R.	25	M	1.75	4,375	4,124	241	3,938	3,734	10	204	5.1	No decompensation; mitral insufficiency
L. D.	18	F	1.4	2,800	2,642	158	993	971	65	22	2	Chronic endocarditis; no decompensation; most of loss of vital capacity due to old paralysis as result of anterior poliomyelitis involving respiratory muscles

* Inasmuch as we have no normal standards for older people, in the case of those over 45 years of age we deduct 10 per cent. from our normal standards, which were obtained from people from 20 to 30 years of age. We believe that this amount of reduction due to age would be approximately correct.

reduced because of an extensive syringomyelia involving her respiratory muscles, which prevented her from sitting up with ease. The reduction of her vital capacity must have been due to this cause, as her heart and lungs were normal.

In the case of L. D., Table 3, the results were totaled in our averages, but we believe much of the loss of her vital capacity was owing to an old paralysis as result of anterior poliomyelitis involving her respiratory muscles rather than to her heart disease.

Finally, Table 4 shows the whole of our series of forty-two patients grouped under what we believe to be their proper classifications and averages. The greatest vital capacity shown by any patient with

TABLE 4.—AVERAGE OF ALL RESULTS ON PATIENTS

	Number of Cases Studied	Average Estimated Normal Vital Capacity of all Patients Studied Sitting, C.c.	Average Actual Determined Vital Capacity of all Patients Studied Sitting, C.c.	Average Percentage Reduction of the Vital Capacity as a Result of Disease	Average Loss in C.c. of the Actual Vital Capacity by Lying Down	Percentage Loss of the Actual Vital Capacity by Lying Down	
Orthopnea of necessity	9	3,989	1,222	69.4	327	26.7	All of these patients fall within our group of the 80% or more of normals who lose a varying degree of their vital capacity on lying down
Orthopnea of choice	14	3,746	1,753	54+	219	12.5	All of these patients fall in the same 80% group
Patients with great reductions of the vital capacity without orthopnea	19	3,757	2,096	36	127	4.7	18.5% of these patients fall into the 20% group or thereabout of normal individuals who increase their vital capacity or do not lose any on lying down

"orthopnea of necessity" (Table 1) was 1,213 c.c., or a 58 per cent. reduction from his estimated normal. The least was 1,107 c.c., or a 78 per cent. reduction from the estimated normal, and this latter case was clinically the most severe instance of orthopnea we have encountered. All cases of "orthopnea of necessity" had an average reduction of 69.5 per cent. from their estimated normal as a result of disease, and on lying down they lost 26.7 per cent. in addition, or one-fourth of their then greatly reduced vital capacity. The cases classified as "orthopnea of choice" (Table 2) showed an average reduction of 55 per cent., due to disease, and they lost on lying down an average of 12.5 per cent., or one-eighth of their reduced vital capacity. The group in Table 3 showed varying degrees of loss of

vital capacity from disease. None of these patients had orthopnea. They had an average reduction in vital capacity of 36 per cent. of the estimated normal, and lost only an additional 4.7 per cent. on lying down.

We have data on about twenty additional cases which for various reasons are not included in this report, but they would not materially alter the results herein recorded. We propose to go forward with the work, and the cases which we now have will form a part of our third contribution on this subject.

The subject matter in our former paper and this one has entailed many figures and much calculating. We have tried to eliminate all errors in totals, but doubtless some small ones have crept in. However, they would in no way invalidate our results.

SUMMARY

1. We conclude from our results that orthopnea can be divided into orthopnea of necessity and orthopnea of choice.

2. Orthopnea cannot exist without reduction of the vital capacity. It the original loss from disease is great and the patient loses an additional amount on lying down, as did 80 per cent. of our normals, there will be "orthopnea of necessity." "Orthopnea of choice" is more common and exists when the original loss from disease is smaller or the percentile loss, as a result of posture, is not so great.

Some patients with as great reduction in their vital capacity from disease as is seen in "orthopnea of necessity" do not become orthopneic. We believe them to be like the 20 per cent. among our 290 normal subjects whose vital capacity was unchanged or increased when they lay down.

We desire to express our thanks to Miss Ruth Trump, our chemical assistant, and Mr. E. J. Warnick, our chief technician, for valuable aid in compiling the data in this paper and our previous one.

THE EFFECT OF OLIVE OIL ON GASTRIC FUNCTION AS MEASURED BY FRACTIONAL ANALYSIS *

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AND
HAZEN G. CHAMBERLIN, M.D.
DETROIT

Olive oil is not uncommonly used in hypersecretory gastric disorders. Most textbooks mention olive oil and infer that its administration lessens the secretion and delays gastric evacuation. References, however, as to proof of its action are few.

Cowie and Munson,[1] in 1908, made an extensive and convincing report on its action. Pawlow, working on dogs, first found that olive oil did not stimulate gastric secretion but actually delayed it. Similarly, on man after the ordinary testmeal extracted at one hour, and after meals with portions extracted at frequent intervals it has been found that olive oil and cotton seed oil when given before meals lessened acidity, delayed the height of secretion and retarded evacuation, while when given after meals it only delayed the height of secretion. These investigators believed its action to be due to coating both the food and mucous membrane, thereby lessening the usual reflex local action of the food on secretion and peristalsis.

Crohn [2] recently reported two observations on the effect of olive oil on the fractional curve. In the first case 2 ounces of olive oil were given immediately after the testmeal and a greater acidity was observed than in the control curve, while the emptying time remained the same. His second observation was made in a case of continual hypersecretion in which 3 ounces of olive oil were given half an hour after the test meal and a diminution of average total acidity from 101.5 to 81.6 degrees was noted. He states that he was disappointed in its action. Two observations, however, are quite insufficient to form any conclusion, especially in view of the variability of the stomach response at different times to the same stimulus.

We have noted clinically that most patients with hypersecretion report improvement after taking olive oil, yet occasionally one is found who does not seem to take the oil well, and complains of increased distress, regurgitation, etc.

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* From the Department of Internal Medicine, Detroit Receiving Hospital.

1. Cowie, D. M., and Munson, J. F.: An Experimental Study of the Action of Oil on Gastric Acidity and Motility, Arch. Int. Med. **1**:61 (Jan.) 1908.

2. Crohn, B. B.: Studies in Fractional Gastric Analysis, Am. J. M. Sc. **155**:801 (June) 1918.

We have observed thirteen patients, seven of whom were considered to have a normal gastro-intestinal tract and six had been found to have an ulcer, either, pyloric or duodenal.

Procedure.—The patient with a morning fasting stomach swallowed the small fractional tube and the fasting contents were aspirated. An Ewald meal was then given with the tube left in place and from 5 to 10 c.c. of contents was aspirated at definite intervals until the return was consistently free of bread. There was noted in each specimen the presence or absence of bread and bile. The free and total acidity was determined by the Toepfer method. All patients were tube broken before securing a control curve, and an effort was made to have them continue on about the same intake of food and water. Within one or two days after securing the control curve another curve was obtained under the same conditions, except that one ounce of olive oil was given

TABLE 1.—SHOWS THE RESULTS IN SEVEN NORMAL CASES FROM ADMINISTRATION OF 1 OUNCE OLIVE OIL FIFTEEN MINUTES BEFORE EWALD MEAL

	Average Free HCl		Average Total Acidity		Maximal Free HCl		Maximal Total Acidity		Evacuation Time			Bile	
Case	Control Curve	Curve after Oil	Control Curve	Curve after Oil	Control Curve	Curve after Oil	Control Curve	Curve after Oil	Control Bread	After Bread	Oil	Control	Oil
A. D.	40	30.5	52	45.7	51	50	66	65	120	180	180+	0	+
A. L.	26.4	17	50.4	29.1	35	34	54	44	100	200	200+	0	+
J. M.	37	27.1	54.2	36.5	56	42	72	55	100	120	120	0	+
P. G.	37.2	30.3	42	43.4	63	44	70	52	120	200	200+	0	+
G. S.	36	36.0	54	46.4	60	52	80	60	80	180	210+	0	+
H. M.	46.2	26.4	66.6	43.1	83	63	98	70	75	105	135	0	0
J. K.	0	0	19	19	0	0	30	35	90	75	100	0	+
Aver.	37.1	27.9	48.3	39.0	58.0	49.1	67.1	54.4	97.8	151.4	163.5		

after the aspiration of the fasting contents and fifteen minutes previous to the Ewald meal. In the specimens of the test curve the presence of olive oil was also noted and an effort made to determine its evacuation time. In more than one half the tests oil was still present in the stomach for a considerable period after the bread had disappeared and the experiment was discontinued.

Results.—In Table 1 are tabulated the results in the seven normal cases observed. As will be noted, the average free acidity was reduced 9.2 degrees after taking the oil and in only one case was the average free acidity as high after taking oil as it was in the control.

The average total acidity was reduced about the same amount (9.3 degrees). In one case it was slightly higher after the oil and in another, an achylia, the average total acidity remained the same.

The high point of free acidity was reduced 8.9 degrees and of total acidity 12.7 degrees. In no case did the maximal free acidity go as high after taking oil as in the control curve, yet in one case the high point of total acidity was slightly higher with oil than without it.

The evacuation time in the controls averaged 97.8 minutes while after oil administration the average stay of bread in the stomach averaged 151.4 minutes, a delay of 53.6 minutes. Oil was still present in the stomach in four of the seven cases for an average time of 163.5 minutes, that is, in the majority of cases it was still present 10 minutes after the bread had left, showing that it is the last to be evacuated by the normal stomach.

Bile regurgitation was not seen in any of the seven control curves, yet in the oil test curves it was observed in one or more specimens in six of the experiments. Figure 1 shows the curves of total acidity representing about the average results seen in this series.

Table 2 shows the results of six observations made on ulcer cases. The average free acidity was lowered 11.6 degrees. However, in one observation (M. G. 2) it was 13.6 degrees higher after taking oil than in the control test.

TABLE 2.—Shows the Results in Six Cases Diagnosed Duodenal or Gastric Ulcer from Administration of 1 Ounce Olive Oil Fifteen Minutes Before Ewald Meal

	Average Free HCl		Average Total Acidity		Maximal Free HCl		Maximal Total Acidity		Evacuation Time			Bile	
Case	Control Curve	Curve after Oil	Control Curve	Curve after Oil	Control Curve	Curve after Oil	Control Curve	Curve after Oil	Control Bread	After Bread	Oil	Control	Oil
M. X.	63.5	50	75	64.5	93	76	110	82	135	180	180	0	+
A. H.	58.2	39.8	66.7	77.8	108	55	140	92	135	180	180+	+	+
H. S.	58.2	44.8	74	59.9	80	62	98	85	120	150	160+	0	0
M. S.	85.8	50.2	96	69	85	80	98	123	105	135	180+	+	+
H. G.[1]	51.2	49.4	67.7	65.5	58	70	78	93	105	135	135	0	+
H. G.[2]	45.4	59	65.1	81	72	87	93	108	135	180	210	0	0
Aver.	60.4	48.8	74.0	69.6	82	71	102.8	97	123	160	175		

The average total acidity was reduced only 4.4 degrees and ran higher in two cases after oil administration.

The maximal free acidity was reduced 11 degrees, yet in two observations (M. G. I. and M. G. 2) the peak of the curve was higher after taking oil.

The maximal total acidity was lowered 5.8 degrees yet in three of the tests the high point after taking oil exceeded the control curve.

The average evacuation time of the bread in the control tests was 123 minutes, after taking oil it was 160 minutes, and the oil still remained in the stomach from fifteen to twenty minutes later in one half the cases.

Bile regurgitation was noted in two of the control curves and in four of the six test curves.

In Figure 2 are shown the curves of total acidity before and after oil administration as observed in patient H. S. This represents the average affect of oil.

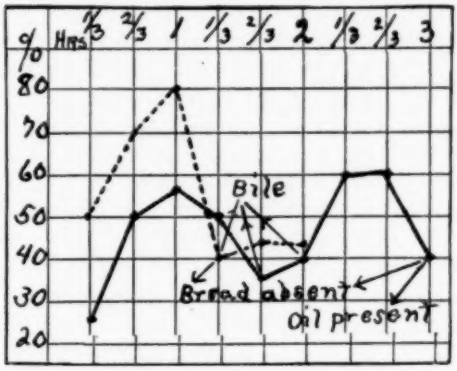

Fig. 1.—Curves of total acidity in the case of G. S. representing average results. Dotted line, control curve; solid line, curve after taking oil.

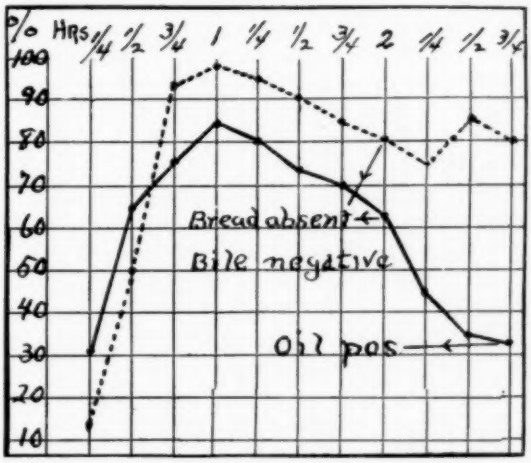

Fig. 2.—Curves of total acidity before and after taking olive oil as observed in H. S. Dotted line, control curve; solid line, curve after taking oil.

In the whole series of thirteen observations, the average free acidity was reduced 9.5 degrees, and in only one of the thirteen cases was it higher after taking oil than before. The average total acidity was reduced 7.8 degrees, and in only three of the thirteen cases was it higher after taking oil. The high point in the curves of free acidity was reduced an average of 10.8 degrees and was higher in only two cases after taking the oil than in the control. The high point of total acidity was reduced an average of 9.1 degrees, yet in four of the cases it ran to a higher point after the administration of the oil. The evacuation time for the bread of the Ewald meal was lengthened about forty minutes, and the oil remained in the stomach an average of at least fifteen minutes longer. Bile regurgitation occurred in ten cases after the use of oil, and in two of the normal controls.

There was no marked difference between the results in normal cases and ulcer cases, except possibly the oil action was slightly greater in the former than in the latter.

SUMMARY

These experiments demonstrate that olive oil given before meals, as is usually done clinically, reduces the average total acidity about 12 per cent., and lowers the high point of the curve about the same degree. It causes a marked delay of the test meal in the stomach and the oil is the last portion of the meal to be evacuated. When oil is given, regurgitation of bile is five times as frequent as without it.

A discussion of the mechanism by which these effects are produced would involve a lengthy discussion of gastric physiology. Our results are similar to those obtained by Cowie and Munson, who attributed the oil action to coating of the food and mucous membrane whereby the usual local reflex action of the food is lessened.

In view of the marked biliary regurgitation (present in ten cases out of thirteen cases following oil administration) it may be well to consider this among the causative factors in our findings.

The presence of bile in the stomach usually means reverse peristalsis. This alone might account for the delay in emptying time. Alkaline duodenal regurgitation might also lower the acidity to the extent found.

Spencer, Meyer, Rehfuss and Hawk [3] believe that duodenal regurgitation is a body defense to protect the small intestine from oncoming irritants. They found trypsin almost constant in the stomach and it was not necessarily accompanied by bile. The higher the trypsin content the lower the acid level. This self regulating action of the pylorus has also been emphasized by Boldyruff.[4]

3. Spencer, Meyer, Rehfuss and Hawk: Effect of Duodenal Regurgitation on Gastric Function, Am. J. Physiol. **39**:459, 1916.

4. Boldyruff, W.: The Self-Regulation of the Acidity of the Contents of the Stomach, Quart. J. Exper. Physiol. **8**:1, 1914.

CONCLUSION

The administration of 1 ounce of olive oil before meals causes a reduction of the average acidity and a lowering of the high point of acidity about 12 per cent. It also causes a delayed evacuation for the bread of an Ewald meal for forty minutes longer than in the control and the oil remains at least fifteen minutes longer. It also causes a regurgitation of bile in about 80 per cent. of cases.

STUDY IN BASAL METABOLISM IN DEMENTIA PRAECOX AND MANIC-DEPRESSIVE PSYCHOSES *

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The idea has long been current that disturbances of metabolism occur in certain mental disorders. Theories of an intoxication, probably endogenous, have often been advanced. Until recently the chemical methods available for clinical application did not afford sufficient evidence to indicate the extent or nature of such disturbances, and there was little to indicate what structures or functions might be involved. The more improved methods of clinical chemistry and the increasing evidence that the ductless glands are involved in many disturbances of growth and metabolism have recently caused a greatly increased interest and activity in the study of such disturbances in patients with mental disease. As a result, there is now some evidence and considerable opinion that disorders of the ductless glands and changes in metabolism may occur in certain psychopathic conditions and psychotic reactions.

Variations in the basal metabolic rate have been found to occur in clinical conditions involving certain ductless glands, especially the thyroid and pituitary. This should, therefore, be a useful method for detecting in psychotic patients disturbances of metabolism in which these glands are involved. Bowman [1] has obtained readings bolew — 10 per cent. in seven of ten patients with dementia praecox. In five of the seven, the rate had increased to — 10 per cent., or higher, at the end of six months.

The observations we here report were made for the purpose of obtaining some idea as to the relation of the mental state of the patient to the basal metabolic rate, while, at the same time, we endeavored to determine in just what clinical types of psychotic reaction, studies in metabolism may be carried on most profitably and controlled appropriately.

Technic.—The observations were made in rooms on the same floor with the ward occupied by the female patients studied. No food was given after the supper at 5:30 the evening before the tests, and the samples were collected from 9:15 to 11 a. m. The female patients

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* From the New York State Psychiatric Institute, and the Medical Clinic, New York Hospital.

1. Bowman, K. M.; Edison, J. P., and Burladge, S. P.: Biochemical Studies in Ten Cases of Dementia Praecox, Boston M. & S. J. **187**:358, 1922.

were kept in bed on the morning of the test, taken to the toilet at 8:30 and then placed in large roller chairs completely recumbent and with sufficient blankets and pillows to insure comfort and warmth. They were then kept under constant observation to secure the necessary rest period and rolled into the room for observation when required. Male patients were dressed, walked down one flight of stairs, across the grounds about 200 yards and up one flight, partially undressed, and placed in the chairs at 8:30.

The apparatus used in determining the basal metabolism was a spirometer of the Tissot type having a capacity of more than 125 liters. Outdoor air was brought into the room by means of a six inch galvanized iron pipe. The inspired and expired air was separated by means of a modified Lovén valve.[2] A gas mask,[3] such as was used by the French Army, was used in the majority of observations in connection with this valve and was found to be more satisfactory than the usual mouthpiece and noseclip, although in many cases both were tried. Not only did the majority of patients have less difficulty in breathing naturally through the mask, many patients almost falling asleep, but the cooperation of the patients became a less important factor so long as they remained physically quiet.

The pulse rate and respiration were counted before, during and after the observation. The average counts are recorded in the tables.

The spirometer was washed out with approximately 15 liters of expired air and the average volume expired per minute was noted. If the patient appeared fairly comfortable and seemed to be breathing naturally, the three-way valve leading to the spirometer was opened at the end of an expiration. The patient was permitted to breathe into the gasometer for six minutes unless the volume expired was abnormally small. In that case the valve was turned off at the end of an expiration after eight minutes. The time was always recorded by a stop-watch. Any physical or mental disturbance on the part of the patient was especially noted.

Samples of air were collected in bottles containing equal parts of glycerin and saturated sodium chlorid solution. The expired air analyses were always done on the day of the observation, with a modification of a Henderson's air analyzer. Analyses of outside air with this apparatus gave averaged valves of 0.03 per cent. for carbon dioxid and 20.91 per cent. for oxygen.

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2. McCann, W. S.: The Effect of the Ingestion of Foodstuffs on the Respiratory Exchange in Pulmonary Tuberculosis, Arch. Int. Med. **25**:850 (July) 1921.

3. Bailey, C. V.: Apparatus Used in the Estimation of Basal Metabolism, J. Lab. & Clin. M. **6**:657 (Sept.) 1921.

In determining the values for carbon dioxid and oxygen in expired air, duplicate analyses checked within 0.04 per cent., except in two cases in which the variation was 0.05 per cent.

Selection of Cases.—The more typical cases of dementia praecox, manic-depressive insanity and psychoneurosis were considered as most suitable, and preferably those in the more active and acute phases, provided sufficient cooperation could be had to meet the requirements of the procedure. Each patient was examined from the standpoint of disordered thyroid and other gland function. The more definite findings of this character which might influence the basal rate are noted in Tables 1, 2 and 3. Except to this extent none of the patients was considered to show gland disturbance of the recognized clinical types which would be expected to influence the rate. To what extent the readings may be accounted for in these terms will be discussed later. None of the cases was considered from routine examination to be complicated by organic disease of the nervous system or other organs except the postencephalitic case in the miscellaneous group, and a trace of albumin and a few casts in the urine, at times, in the first case in the manic-depressive group.

The cases were observed on the Psychiatric Institute Service and were carefully considered from the standpoint of clinical grouping by Dr. Geo. H. Kirby, director of the institute.

Cooperation.—The requirements of the test are physical and mental rest and relaxation to secure a basal level. If the physical factor can be secured then variations in the mental factor can be considered in relation to the basal rate. The notes in the tables as to cooperation refer to the physical requirements, primarily the control of motor activity during the test and the preliminary rest period, and to the respiration. The term "satisfactory" designates a degree of physical cooperation comparable to that of the average nonpsychotic patient. In some cases, especially the retarded depressions, there was even less motor activity than normal. In those noted as "restless" there was some shifting or turning in the chair or moving of the head and arms, in some instances accompanied by talking. Further observations are necessary to determine just how much the rate is influenced by the motor activity and such disturbances of respiration as occur in mildly restless patients. In some of the readings the variations of this kind were considered to be so small that the reading could be classed as satisfactory. These readings are noted as satisfactory, but with the addition of notes to indicate the presence of slight variations. Less satisfactory readings are indicated by the notes. Where the reading was quite evidently influenced by motor activity the reading has been enclosed in brackets.

Mental cooperation by psychotic patients to the extent of mental quietness or relaxation in the same sense as in nonpsychotic or nonneurotic patients is of course quite difficult to obtain or even to estimate accurately. The psychic factor, the mental or emotional state or tension, in relation to the basal rate has been considered in two ways, assuming that motor activity is controlled. First, as a separate factor influencing the rate directly, and second, as a part of the total clinical picture of the psychosis. That is, whether the rate would vary with the character and intensity of the mental and emotional state at the precise time of collecting the sample, or would be more closely correlated with the clinical type of psychotic reaction as shown by the symptoms and behavior from day to day. It would now seem that the demonstration of a direct relation between the rate and the mental state at the time would require quite careful psychologic observations and a degree of cooperation which cannot be had from the types of patients who have shown the greatest variation from the normal rate. It would also probably be essential to separate the mental state into several factors including the mental content, or what the patient was thinking about, and the character and intensity of the emotional reaction both subjectively and objectively. A direct psychic or emotional influence on the rate to an extent requiring such observations at the precise time of determining the rate would suggest a considerable degree of lability and responsiveness by the rate to such stimuli. It is of interest here to note the increase in the basal rate following the subcutaneous injection of 0.5 c.c. of epinephrin,[4] which suggests an increased rate in primitive emotional reactions like fear, as described by Cannon and by Watson. A similar and sustained response of the organism to prolonged emotional stimuli of this kind would, however, seem more problematical. And, unfortunately, the complex emotional factor in psychotic reactions is often quite difficult of estimation and expression in these terms. In the cases here reported the consistency of consecutive readings on the same patient speaks against a responsiveness by the basal rate to any factor which can be considered separately and independently from the total clinical condition from day to day. It remains, therefore, to consider the rate in relation to the clinical reaction types into which the cases fall and what factors or symptoms in the clinical picture it can be correlated with.

MANIC-DEPRESSIVE GROUP

The manic-depressive cases are arranged in Table 1 somewhat according to the basal rate, with the lowest at the top. The first seven cases were typical of depression. The first four cases were recent admissions, and quite comparable clinically, had shown little or no

4. Sandiford: Am. J. Physiol. **51**:407, 1920.

TABLE 1.—MANIC-DEPRESSIVE GROUP

	Psychomotor	Emotional	Date, 1922	Basal Rate, per Cent.	Cooperation	T.	P.	R.	Weight, Lbs.	Height, M.	Surface Area Ht.-Wt. Formula (DuBois)	Volume Expired Liters per Hour	Gas Analysis		Calories per Hour	R. Q.
													CO_2 per Cent.	O_2 per Cent.		
No. 1. Depressive; male 53; Adm. 1/31/22; previous attacks, 3; manic type; gradual improvement during period of these observations	Inactive; retarded; quiet	Depressed; looks distressed; no tears	2/15	—13	Satisfactory	98	60	14	147	1.77	1.82m²	292.0	3.44 3.42	16.87 16.87	59.18	0.809
			2/16	— 8	Satisfactory	98	59	18	147	....	1.82m²	279.3	3.20 3.21	16.70 16.68	63.04	0.709*
			2/20	—15	Satisfactory	98	54	19	148	....	1.82m²	290.5	3.33 3.33	16.94 16.92	58.00	0.795
			3/20	—11	Satisfactory	98	54	16	145	....	1.81	360.1	2.76 2.75	17.60 17.56	60.19	0.782
No. 2. Depressive; male 29; Adm. 2/4/22; previous attacks, none; no thyroid signs; thyroid, 2 gr. daily, 3/10; no improvement noted	Fairly active but retarded; quiet; keeps occupied in a slow way	Depressed; sad, distressed expression; many tears	2/24	—13	Satisfactory	98	48	15	147	1.77	1.82	403.2	2.51 2.50	17.82 17.83	62.51	0.765
			2/27	— 9	Satisfactory	98	52	16	147	....	....	426.0	2.86 2.84	17.88 17.90	64.92	0.919
			3/ 1 thyroid	—12	Satisfactory	98	53	15	147	....	....	430.8	2.70 2.70	17.78 18.01	63.23	0.900
			3/22	— 3	Satisfactory	98	48	20	149	....	....	468.5	2.56 2.56	17.96 17.96	69.74	0.826
No. 3. Depressive; female 57; Adm. 3/11/22; previous attacks, 2	Inactive; retarded; quiet	Depressed few tears	3/21	—11	Satisfactory	98[6]	88	11-19 irreg.	161.5	1.64	1.79	348.1	2.45 2.45	17.69 17.73	55.79	0.714*
			3/25	—11	Satisfactory	99[2]	82	17	162.5	....	....	364.3	2.40 2.41	17.86 17.89	55.48	0.744
No. 4. Depressive; female 45; Adm. 1/19/22; previous attacks, 3; skin dry, glossy, yellowish, thin; hair dry; brows thin; thyroid, 2 gr. daily 3/12; no definite improvement noted	Inactive; retarded; quiet; wants to stay in bed	Depressed; sad expression but smiles feebly at times; no tears	2/21	— 9	Satisfactory	98	72	12	125	1.65	1.61	309.6	2.85 2.84	17.52 17.49	52.82	0.796
			2/23	—15	Satisfactory	98.4	72	11	125	....	1.61	272.0	3.00 3.00	17.35 17.33	48.81	0.798
			3/ 2 thyroid	— 8	Satisfactory	98.2	66	15	123	....	1.60	307.9	2.79 2.79	17.49 17.48	52.78	0.771
			3/21	— 2	Satisfactory	98	60	15	123.5	....	1.60	319.1	2.95 2.94	17.39 17.42	56.17	0.800
No. 5. Depressive; female 33; Adm. 3/27/22; previous attacks, 2	Inactive	Depressed; suicidal	3/29	— 6	Moved several times; after mask was removed cried and said she was afraid	98	60	16	127	1.68	1.64	357.9	2.69 2.70	17.80 17.77	56.32	0.823
No. 6. Depressive; male 41; Adm. 1/26/22; previous attacks, 1; manic type; improved since adm.	Inactive; quiet; slightly retarded	Depressed; stolid expression; no tears	2/ 2	— 6	Satisfactory	98.8	63	12	149.5	1.79	1.84	323.7	3.78 3.76	16.82 16.84	66.48	0.868
			2/ 6	— 3	Satisfactory	98.2	62	10	151	....	1.84	346.4	3.69 3.67	16.93 16.94	69.18	0.902
No. 7. Depressive; postpartum; female 41; Adm. 9/24/21; previous attacks, 2, each postpartum; now much improved; underweight 15 pounds, but gaining	Inactive; quiet	Depressed; unstable; smiles easily at times	2/ 7	— 6	Satisfactory	98.4	84	16	86.5	1.59	1.34	229.4	3.13 3.11	16.94 16.97	45.28	0.743
			2/11	+ 3	Satisfactory	98.2	78	16	88	....	1.35	272.4	3.21 3.16	17.23 17.26	50.08	0.835

ed; underweight 15 pounds, but gaining																
No. 8. Mixed; female 19; Adm. 1/4/22; previous attacks, none	Usually quiet; outbursts of overactivity; at times mute and semi-stuporous	Marked variability	2/ 3	— 6	Satisfactory	97.2	82	16	98.5	1.67	1.47	246.5	3.48 3.49	16.68 16.65	52.31	0.781
			2/ 9	(+ 9)	Not satisfactory; restless; muscles tense at times	99	88	20	95	....	1.45	335.0	3.01 3.01	17.17 17.18	62.49	0.762
			2/25	— 6	Satisfactory; restless before tests	98	76	20	99	....	1.47	387.7	2.53 2.52	18.23 18.26	52.24	0.920
			3/ 9	—10	Satisfactory; crying before test	97.8	80	20	105	....	1.51	367.5	2.62 2.61	18.13 18.09	51.90	0.910
No. 9. Manic; now hypomanic; female 33; Adm. 2/11/22; previous attacks, none; thyroid slightly enlarged, nodular	Overactive; restless	Elated; short periods of depression	3/ 7	— 8	Satisfactory	98.6	57	14	97	1.61	1.42	219.2	3.62 3.61	16.58 16.56	47.66	0.794
			3/ 9	—15	Satisfactory	98.8	63	16	97	....	1.42	266.2	3.14 3.13	17.60 17.64	44.15	0.935
Much improved, with gain in weight at time last readings were made	Less active	More emotional and tearful at time of last readings	4/20	+ 7	Satisfactory	98.8	72	13	120	....	1.55	316.8	3.13 3.13	17.12 17.12	60.43	0.779
			4/21	+ 5	Satisfactory	98.6	73	13	120	....	1.55	316.3	3.11 3.11	17.18 17.18	59.16	0.791
No. 10. Manic; now hypomanic; female 19; Adm. 11/3/21; previous attacks, one	Overactive	Mild elation	2/16	— 6	Restless before test; quiet during test	98.8	70	25	128	1.55	1.55	380.6	2.40 2.41	18.02 18.04	55.10	0.793
			2/21	+ 1	Restless before test; quiet during test	98.8	106	24	126	....	1.54	398.5	2.42 2.44	17.93 17.94	59.30	0.774
			2/28	— 8	Satisfactory	98.4	72	28	124.5	....	....	381.6	2.37 2.41	18.12 18.10	53.69	0.813
No. 11. Circular; now hypomanic; female 48; Adm. 5/17/19; previous attacks, one; depression postpartum	Overactive	Elated; irritable	2/16	— 3	Satisfactory	98.2	58	16	174	1.67	1.87	290.3	3.63 3.62	16.44 16.42	65.06	0.766
No. 12. Manic; now hypomanic; female 19; Adm. 2/28/22; previous attacks, one, circular	Overactive	Elated	3/ 4	+ 4	Restless before and during test; moved hands some	98.2	69	12	148	1.56	1.66	315.6	3.24 3.26	16.75 16.76	65.41	0.735
			3/ 7	— 1	Restless before and during test	98	58	13	144.5	....	1.64	299.2	3.31 3.32	16.78 16.80	61.61	0.762
No. 13. Mixed; female 30; Adm. 7/21/17; agitated; previous attacks, 3	Overactive; agitated	Depressed, with anxiety and apprehension	3/14	+ 6	Restless, apprehensive; pulse and respiration constant	98	72	12	118.5	1.53	1.49	356.6	2.66 2.64	17.69 17.71	57.40	0.782
			3/16	+ 2	Restless, apprehensive; pulse and respiration constant	99.4	63	20	118	....	....	359.7	2.81 2.81	17.85 17.83	55.49	0.886
No. 14. Depressive; agitated; male 41; Adm. 10/11/21; previous attacks, none	Overactive; muscle tonus increased; agitated	Depressed; distressed; sad, agitated	2/24	+ 5	Satisfactory	98	70	16	126	1.72	1.67	403.4	3.05 3.05	17.56 17.58	67.51	0.889
			2/27	+ 7	Satisfactory; hand clenched	98	92	18	127	....	....	440.7	2.74 2.73	17.78 17.80	69.07	0.843
No. 15.* Mixed; now hypomanic; female 39; Adm. 10/28/21; previous attacks, 3; thyroid palpable, not enlarged; much improved since admis.	Overactive; works all day	Constantly elated and smiling	3/11	+35	Satisfactory	98.6	102	15	107	1.58	1.47	426.5	2.92 2.89	17.52 17.53	72.36	0.819
			3/21	+20	Satisfactory	98.6	88	17	111	....	1.49	391.6	2.76 2.77	17.62 17.58	64.94	0.796

TABLE 2.—DEMENTIA PRAECOX GROUP

	Date, 1922	Basal Rate, per Cent.	Cooperation	T.	P.	R.	Weight, Lbs.	Height, M.	Surface Area Ht.-Wt. Formula (DuBois)	Volume Expired Liters per Hour	Gas Analysis CO_2 per Cent.	Gas Analysis O_2 per Cent.	Calories per Hour	R. Q.
No. 16. Male 17; Adm. 2/1/22; depressive; delusional; quiet; apprehensive, fearful; soon after became actively suicidal on delusional basis, requiring restraint and constant watching; slightly emaciated; pale; Hgb. 85%; history of very rapid growth	2/10	—25	Satisfactory, apprehensive and nervous	98	76	19	90	1.64	1.40m²	211.2	3.25 3.26	16.65 16.62	45.10	0.72
	2/14	—32	Satisfactory, somewhat apprehensive	98	60	21	90	....	....	220.0	3.09 3.08	17.21 17.22	40.74	0.792
	2/15	—24	Satisfactory, apprehensive	98	66	19	91	....	....	236.3	3.40 3.38	16.87 16.87	45.85	0.798
No. 17. Female 16; Adm. 10/28/20; catatonic type; usually mute; wets and soils at times; eats ravenously; well nourished; childish appearance; sex development retarded, has menstruated only one time; thyroid full, possibly slightly enlarged; Pulse 120-130 at times	2/ 3	(+ 9)	Not satisfactory, tried to sit up	99	112	16	91	1.59	1.37	369.6	2.80 2.79	17.28 17.28	59.79	0.722
	2/ 9	—17	Satisfactory	98	96	16	90.5	....	....	286.9	2.63 2.63	17.73 17.74	45.55	0.787
	2/11	—23	Satisfactory	98	84	15	88.4	....	1.35	256.5	2.95 2.94	17.38 17.41	41.72	0.797
No. 18. Female 19; Adm. 1/31/22; hebephrenic type; childish appearance; wets and soils; bed wetter for past two years; profane; thyroid slightly and uniformly enlarged; amenorrhea since admission	3/11	—21	Fairly satisfactory; talked at end but volume remained constant	98.2	60	19	100	1.49	1.37	278.1	2.64 2.64	17.99 18.01	40.7	0.877
	3/29	(—10)	Not satisfactory, moved constantly, talked	97.4	60	16	96.5	....	1.34	268.0	2.76 2.77	17.47 17.49	46.06	0.761
No. 19. Male 29; Adm. 2/28/22; catatonic; mute; inactive; spoon fed; increased muscle tonus; prison record	3/ 6	—10	Satisfactory	98.4	60	12	118.5	1.73	1.63	318.6	2.90 2.90	17.37 17.37	56.48	0.775
	3/ 8	—17	Satisfactory	98.8	60	11	118.5	....	....	303.7	2.97 2.97	17.38 17.34	53.64	0.803
Before last reading symptoms became more pronounced; tube fed; muscle tonus greatly increased	3/28	— 5	Satisfactory	99.4	80	18 irreg.	114.5	....	1.61	348.4	2.84 2.80	17.45 17.43	60.62	0.796
No. 20. Female 36; Adm. 2/25/21; paranoid, depressive; depressed; not definitely agitated; overactive, constantly at work	3/14	—16	Not satisfactory; restless, afraid, crying before test; quiet 15 min. before and during test	97.4	59	26	96.5	1.51	1.35	310.5	2.62	18.29	41.23	0.985

	3/18	−13	Fairly satisfactory, apprehensive; pulse and respiration regular and normal	97.4	48	18	97	. . .	1.36	246.7	2.79 2.77	17.40 17.42	43.17	0.747
No. 21. Female 26; Adm. 11/9/21; paranoid type; usually quiet and inactive; perplexity, emotional variability; objective symptoms improved since admission	2/ 3	−16	Fairly satisfactory; quiet; uneasy; wanted to hold breath	98.2	80	12	97	1.61	1.42	192.5	3.75 3.77	16.31 16.34	44.11	0.779
	2/ 9	(+ 9)	Not satisfactory; restless; respiration uneven	98.6	80	15?	97.5	....	....	289.2	3.45 3.46	16.98 16.96	57.18	0.842
	2/16	− 4	Satisfactory	98.6	72	12	97.5	....	....	287.8	2.90 2.90	17.39 17.38	50.80	0.790
	3/ 2	− 9	Satisfactory; restless before test	98.4	64	17	92.7	....	1.40	246.3	3.18 3.15	17.13 17.13	46.72	0.798
No. 22. Male 19; Adm. 2/28/22; paranoid type; quiet; seclusive, apprehensive	3/ 6	−12	Satisfactory	90	60	20	120	1.68	1.60	391.5	2.36 2.34	17.88 17.92	59.05	0.730
	3/ 8	− 9	Satisfactory, somewhat restless before test	99.2	68	26	118	....	....	449.3	2.17 2.17	18.27 18.28	59.30	0.781
No. 23. Male 17; Adm. 12/23/21; paranoid type; inactive; quiet; partial insight; improved since admission	3/ 3	− 5	Satisfactory	98	72	14	129.5	1.61	1.60	336.3	3.37 3.38	17.03 17.08	65.16	0.840
	3/13	−10	Satisfactory	98.8	60	11	129.5	....	....	320.4	3.53 3.52	17.10 17.09	61.57	0.898
No. 24. Male 16; Adm. 9/29/21; hebephrenic type; admitted after episode of excitement; improved since admission; now seclusive, smiling; marked cyanosis and sweating of hands	2/ 6	− 5	Satisfactory	98.2	76	12	119.5	1.64	1.58	277.6	4.07 4.09	16.29 16.33	64.05	0.855
	2/10	− 8	Satisfactory	98	72	17	122	....	....	291.5	3.65 3.69	16.61 16.66	62.21	0.819
No. 25. Male 23; Adm. 5/1/21; paranoid type; overactive; euphoric; psychopathic; criminal history	2/15	+12	Fairly satisfactory; quiet; uneasy, fingers moved constantly during test	98	80	13	114.5	1.66	1.56	284.3	4.28 4.28	16.07 16.08	68.87	0.854
No. 26. Male 21; Adm. 1/7/22; paranoid type; periods of overactivity and excitement; first reading followed and last reading just preceded these disturbed periods	2/ 2	+16	Satisfactory	98.2	81	16	123	1.68	1.62	342.6	3.40 3.43	16.60 16.59	73.82	0.747
	2/ 8	+11	Satisfactory	98	74	15	122	....	1.61	304.3	3.77 3.77	16.25 16.27	70.62	0.768
	3/15	+17	Satisfactory	98	79	18	115	....	1.58	435.7	2.84 2.84	17.54 17.58	73.29	0.807

improvement when these observations were started, cooperated well, and showed rather consistent readings which averaged — 11.2 per cent. The fifth patient did not cooperate well. The sixth and seventh patients were much improved and showed readings more nearly normal. In Case 9 the manic attack was accompanied by considerable loss of weight. The first readings, — 8 and — 15 per cent., respectively, were made soon after the patient was quiet enough to cooperate. There was rapid improvement with gain in weight. The last readings were made just as the patient was ready to go home, and were + 7 and + 5 per cent. respectively.

In Case 15 there were no very definite signs of hyperthyroidism, although the readings were + 35 and + 20 per cent. Since admission the emotional reaction has been objectively quite marked. At first she cried easily and showed a flushed face, and is now quite definitely and genuinely elated.

Two patients (Cases 13 and 14) showed the agitated type of depression, but cooperated sufficiently well to indicate that their agitation did not raise the rate above the normal limits, although it may have kept it from being as low as in the simple depressions.

In the manic-depressive table there has been set out in separate columns a rough estimate of the psychomotor and emotional factors in the clinical picture as shown from day to day. Study of these in relation to the rate indicates that further observations are necessary to determine whether any very close relation exists between these factors and the basal rate, and that one cannot be considered without the other. In addition to the question of cooperating, it should also be borne in mind that a hypomanic state may represent a transient or rather convalescent phase of the psychosis, and for this reason may not be comparable to the more marked manic or depressed states. Gains in weight have been noted in some such cases.

If, as is indicated by these findings, the rate is slightly decreased in depressions, it should probably not be concluded that the basal rate is influenced in the same way in individuals suffering from emotional disturbances but who have not become psychotic. Many of these manic-depressive attacks seem to be clearly precipitated by emotional and other influences similar to those found in the history of many cases of exophthalmic goiter, while in others it is apparently impossible to establish a relation between an emotional disturbing cause and the mental break-down.

DEMENTIA PRAECOX GROUP

Cases which were considered to be essentially and fundamentally of the schizophrenic type have been included in Table 2. As previously

indicated, there was not enough evidence of disturbed endocrine function to explain these definitely abnormal rates in terms of recognized clinical types, i. e., as hypothyroid or hyperthyroid or pituitary. Skin evidence of myxedema was not found in any case in this group. There was no adiposity nor definite infantilism. Evidence of growth disturbance was, however, present in some. One patient (Case 16) gave a history of recent very rapid growth. Another (Case 17) had not attained physical sex maturity and had had a single scanty menstruation. One (Case 18) would probably be classed as polyglandular. None of the males was very definitely deficient in gross gonadal development, and in most of them, including Case 16, it was equal to the adult average. Several patients showed deficient or perverse secondary sex features. In the light of present evidence these lesser degrees of disturbed development of bone, muscle, and the physical characteristics of sex probably cannot be expressed in terms of any one gland. Adequate function of several glands seems to be necessary for complete physical maturity. Therefore, the most that can be said as to their relation to metabolism is that some of the cases show this much evidence of a disturbance of an "endocrine" nature. Some evidence as to the frequency of imperfect and retarded sex development in cases with early onset will be presented by one of us (Gibbs) in another paper.

Starvation or undernutrition does not seem to explain the findings except possibly to some extent in Cases 16 and 19. These patients were poorly nourished and there was some question of restriction of food intake due to an inclination to refuse food. The extent of this could not be determined. None of the others was definitely undernourished. One patient (Case 17) had required to be spoon-fed when admitted in 1920 but for several months had eaten ravenously her own food and that of other patients and was well nourished.

One boy (Case 16) presented several features which suggested a more profound disturbance of metabolism than simple inanition as the cause of the low readings, which averaged —27 per cent. In October, 1920, soon after the patient was 16 years of age, this boy had left his position and found work elsewhere because he thought the girls in the office where he worked were laughing at him. Later he felt too weak to work, and finally in August, 1921, he quit work entirely, and definite ideas of reference were noted. Fear was said by his mother to be a dominating symptom for a year before his admission. After September, 1921, he would not leave the house and was very fearful. In October, 1921, he began to grow so rapidly as to require new clothing. This was associated with a voracious appetite, especially for sweets. About Christmas, 1921, severe headaches developed, appetite became poor and bowels constipated. This continued until February when an acute delusional episode with an attempt at suicide caused admission to the hospital, Feb. 4, 1922.

He was thin, and the muscular wasting, or lack of development, seemed slightly out of proportion to the loss of subcutaneous fat. The thyroid was palpable at the isthmus, but was thought to be small. There was no appearance of myxedema. The testes were of the average adult size with a fair growth

of pubic hair of masculine type. No hair on chest or face. Had to be spoon-fed. Said he could not eat because bowels were stopped up and stomach was full. Bowels moved daily voluntarily or by enema. This was the status when the basal rate determinations were made. There was no loss of weight during the five days between the first and last determinations. February 21 a twenty-four hour urine of 1,250 c.c. contained 3 gm. creatinin and 387 mg. creatin (Folin method, creatinin-zinc chlorid standard). March 2 a twenty-four hour urine of 1,015 c.c. contained 1.349 gm. creatinin and 172 mg. creatin with a total nitrogen of 7.32 gm. (Kjeldahl). February 17 the fasting blood sugar was 112.4 mg. per 100 c.c. (Folin), and forty-five minutes after the ingestion of 80 gm. of glucose it had risen to 230 mg. Sugar did not appear in the urine (Benedict).

Further observations could not be made because the patient became so actively suicidal in response to his delusions as to require constant restraint in a protection sheet. Thyroid, 2 grains daily, was given from March 9 to March 19, but produced no appreciable effect and was discontinued because of a loss in weight. Restraint continued to be necessary. April 15 the hands and forearms were markedly cyanotic and cold, and passive motion at the elbows was difficult because of greatly increased muscle tonus. Tube fed twice daily. Anterior pituitary (Armour), ¼ grain daily, with one of the meals was begun, since which time gradual increase in food intake with gain in weight has been noted. May 5 he was taking his food voluntarily; muscular tension has relaxed and cyanosis almost gone.

The cases are too few to attempt correlations between the rate and the clinical picture as a whole or separate symptoms or factors. Just how much the rate varies with the clinical picture, with the quiet and disturbed phases, the fluctuations in weight, appetite, and behavior, which some of these patients show must be the subject of further careful observations, following the same patient through these changes. In the cases studied those which seemed to be in the more active or acute phases of the reaction also showed the greatest variation from the normal rate. In Case 19, however, it was noted that with an increase in the severity of symptoms, the rate became more nearly normal. Two factors may have influenced it, the greatly increased muscle tonus or the increased protein in the tube-fed meals of milk and eggs which the patient had been receiving for three days before the last reading.

Correlation between the basal rate and the psychomotor and emotional factors has not been attempted in this group, since they are in many cases so much more difficult of description, evaluation, and classification than in the affective group. In certain of the dementia praecox cases with a definite emotional coloring the basal rate showed quite definite variations from normal. In Case 16 there was marked depression and apprehension on a delusional basis, while in Case 26 there were periods of excitement and over-activity and an increased rate just following and preceding such periods. In other cases however (Cases 17 and 18), the emotional factor was not prominent, and there were also definitely low readings.

MISCELLANEOUS AND CONTROL GROUP

Case 27 was not included in the dementia praecox group because some doubt remains as to the essential nature of the psychosis. The patient recovered from the first episode with apparently complete insight. The diagnoses made at the time are indicated in Table 3. The clinical picture at the time the readings were made was one of depression. The readings were lower than in the simple depressions and the rate was not raised by thyroid, suggesting the possible presence of some constitutional factor not present in the simple depressions.

There is also some question as to the diagnosis of cases classed as psychoneurosis. They have been introduced as control cases for the reason that they were in a settled chronic state rather than an acute phase of their psychosis. Cases of psychoneurosis which would afford a satisfactory basis for comparison with neurotic types usually regarded as nonpsychotic were not available in the hospital at the time these observations were made.

Three nurses and one physician who served as controls gave normal readings, while one nurse and one physician gave abnormal readings, the evidence for which is shown in the tables.

The discussion in this paper has probably gone into more detail than is warranted by the data. It may be justified by bringing out some of the points to be considered, especially that in functional studies of this character interpretation of the findings must be made in the light of the clinical state or phase presented by the patient at the time. Some of the reports on biochemical studies in the functional psychoses indicate that this has not always been considered. The work of Folin [5] on metabolism in mental disorders has been subjected to this criticism by Pighini and Statuti.[6] It is of interest to note that while the work of Folin was quite exhaustive on the chemical side, the selection of cases and limited clinical observations prevented correlations between the chemical findings and the acute and chronic phases. The seven dementia praecox cases studied were all in the chronic phase. If there are abnormal variations in the metabolism in dementia praecox it would seem probable that such changes would be most marked and therefore most tangible and appropriate for study in the more active and acute phases of the process. Pighini and Statuti found an excessive elimination of nitrogen, phosphorus, and unoxidated sulphur in all of six cases of dementia praecox in an acute exacerbation. Benedict [7] recently suggested a close relation between nitrogen loss and decreased basal rate.

5. Folin: Am. J. Insanity **60**:699, 1904; **61**:299, 1904.

6. Pighini and Statuti: Metabolism in Dementia Praecox, Am. J. Insanity **67**:299, 1910.

7. Benedict: Metabolism During Starvation and Undernutrition, New York M. J. **115**:249 (March) 1922.

TABLE 3.—Miscellaneous and Control Group

	Date, 1922	Basal Rate, per Cent.	Cooperation	T.	P.	R.	Weight, Lbs.	Height, M.	Surface Area Ht.-Wt. Formula (DuBois)	Volume Expired Liters per Hour	Gas Analysis		Calories per Hour	R. Q.
											CO_2 per Cent.	O_2 per Cent.		
No. 27. Male 16; Adm. 8/16/21; D. P. (case not clear); paroled 11/23/21; psychosis with psycopathic personality; paranoid hallucinatory episode; recovered. Returned to hospital 2/18/22; depressive; rapid growth 6 months prior to first admission; anti-social behavior beginning at 13 years; fear seems to be a prominent factor; quiet; inactive	2/24	—14	Satisfactory	98	60	20	109	1.57	1.47m²	378.8	2.35 2.35	18.04 18.07	54.13	0.781
	2/27*	—19	Satisfactory	98	60	20	109.5	....	....	373.2	2.37 2.35	18.17 18.22	50.97	0.831
	3/22	—17	Satisfactory	98	52	21	104	....	1.44	402.8	2.25 2.26	18.39 18.36	51.29	0.859
No. 28. Male 13; Adm. 2/2/22; postencephalitis psychosis; overactive, talkative; adipose; some hypopituitary features, but gonodal development precocious, with feminine pubic hair	3/ 3	—20	Satisfactory	98	69	24	142	1.67	1.71	443.9	2.76 2.79	17.83 17.86	64.44	0.865
	3/13	—16	Satisfactory	99²	76	22	142	....	....	450.5	2.75 2.72	17.73 17.76	71.80	0.825
No. 29. Female 28; Adm. 12/19/19; psychoneurosis, anxiety type; masculine hair growth; history of pelvic operation	3/24	+ 7	Fairly satisfactory; restless before, quiet during test	98.8	96	14	95	1.48	1.32	291.1	2.91 2.93	17.31 17.31	52.44	0.766
	3/27	— 4	Satisfactory	98.6	84	13	95	....	....	277.0	2.71 2.69	17.53 17.56	46.63	0.756
No. 30. Psychoneurosis, neurasthenic type; female 42; adm. 12/31/21; previous admission, one	3/24	± 0	Satisfactory; breathing irregular	97.8	96	25	72.5	1.54	1.225	372.4	1.94 1.96	18.54 18.57	44.04	0.783
No. 31. Psychoneurosis, psychasthenic type; female 41; Adm. 1/20/15; masculine hair growth	3/27	— 4	Satisfactory	98.6	82	19	101.5	1.56	1.47	350.1	2.33 2.33	18.02 18.04	50.57	0.761
	3/28	— 8	Satisfactory	98.2	66	22	...	....	....	356.8	2.28 2.31	18.21 18.21	48.44	0.809
Dr. H., age 27	3/20	+ 5	Satisfactory	98.4	80	11	125	1.63	1.60	397.2	2.87 2.90	17.59 17.59	66.31	0.833
Miss F., nurse, age 18	3/17	+ 4	Satisfactory	98.4	80	24	132	1.55	1.57	393.9	2.79 2.79	17.60 17.62	65.26	0.804
Miss M., nurse, age 22	3/17	+ 2	Satisfactory	98	72	20	138.2	1.56	1.61	344.5	2.89 2.88	17.42 17.40	60.51	0.781
Miss H., nurse, age 23	3/10	+ 5	Satisfactory	98.2	76	24	128.8	1.60	1.60	386.5	2.63 2.62	17.72 17.72	61.82	0.780
Miss L., nurse, age 23; several attacks tonsillitis; 20 lbs. underweight; fine tremor fingers; thyroid doughy, possibly slightly enlarged	3/10	+25	Satisfactory	98.2	68	16	126.3	1.61	1.59	317.2	3.81 3.83	16.29 16.33	73.04	0.789
Dr. B., age 33; adipose	3/22	—16	Satisfactory	98	60	11	181.5	1.74	1.96	363.4	3.07 3.04	17.36 17.33	65.09	0.816

* Thyroid, 2 gr. daily, 3/10 to 3/21.

SUMMARY

1. Definitely abnormal basal rates were found in psychotic patients in the more acute phases of their psychosis. The variations from normal were greater in dementia praecox patients than in manic-depressive insanity.

2. The patients did not show sufficient evidence to explain satisfactorily the findings in terms of thyroid or pituitary disorder. Several of the dementia praecox patients did show some evidence of disturbed growth, including incomplete sex maturity.

3. Thyroid by mouth raised the rate to normal in two cases of manic-depressive depression, but did not in a case with more marked constitutional psychopathic features. No immediate mental improvement followed thyroid in these three cases.

4. Inanition was not thought to account for the low readings except possibly to some extent in two cases. In one of these there was found a creatinin excretion of 33 mg. per kilo, with 172 mg. creatin, in twenty-four hours, and in the other a creatinin excretion of 26.8 mg. per kilo, with 195 mg. creatin, in twenty-four hours.

5. In functional studies in the psychoses the findings should be considered in relation to the symptoms and phases or stages presented by each patient as well as to the clinical group to which he belongs.

* Thyroid, 2 gr. daily, 3/10 to 3/21.

HIPPURIC ACID SYNTHESIS AS A TEST OF RENAL FUNCTION *

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OMAHA

The worth of an organ is measured by its capacity to perform the daily task, in other words, by its physiologic efficiency. This idea of the fundamental importance of the patency of the organ underlies the many attempts to discover means of assaying the functional capacity of the affected organ. The kidney, on whose integrity an individual's welfare depends to a large extent, has been the object of the greatest number of functional tests. The tests most in vogue in clinical medicine fall into several groups depending on the particular task which each purports to present to the kidney. One of the most commonly employed tests is concerned with the ability of the kidney to rid the body of a foreign body, such as the dye phenolsulphonephthalein.[1] Others attempt to place the kidney under an increased strain in performing its excretory function, by increasing very greatly the amount of sodium chlorid,[2] of uric acid [3] or urea [4] and finding out how well the kidney measures up to the expectation under the strain. Inasmuch as the kidney is an organ of considerable structural complexity, with great possibilities for compensatory rearrangement of the functional load, Mosenthal's method,[5] involving a survey of various aspects of the kidney physiology, comes closer, perhaps, to giving an insight into the condition of this organ than any other test, but, as was pointed out recently by Rabinowitch,[6] no single test is reliable and the responses to each test vary with the type of nephritis.

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1. Rowntree, L. G., and Geraghty, T. J.: An Experimental and Clinical Study of the Functional Activity of the Kidneys by Means of Phenolsulphonephthalein, J. Pharmacol. & Exper. Therap. **1**:579, 1910.

2. Kummer, R. H.: L'appréciation des fonctions rénales par l'alterance des éliminations ureo-chlorurées ainsi que par le bilan chloruré au cours de la chlorurie expérimentale, Presse méd. **29**:603, 1921.

3. Magath, T. B.: A Test for Early Renal Insufficiency, J. Lab. & Clin. M. **6**:463, 1921.

4. MacLean, H., and de Wesselow, O. L. V.: On the Testing of Renal Efficiency with Observations on the Urea Coefficient, Brit. J. Exper. M. **1**:53, 1920.

5. Mosenthal, H. O.: Renal Functions as Measured by the Elimination of Fluids, Salts and Nitrogen, and the Specific Gravity of the Urine, Arch. Int. Med. **16**:733 (Nov.) 1915.

6. Rabinowitch, I. M.: The Urea Concentration Test for Kidney Function, Arch. Int. Med. **28**:827 (Dec.) 1921.

Ever since Bunge and Schmiedeberg [7] demonstrated in their experiments on dogs that hippuric acid is synthesized in the kidney from benzoic acid and glycocol, the ability of this organ to effect such conjugation has been investigated extensively as a means of determining the extent of renal injury. It stands to reason that if the hippuric acid synthesis is a specific function of the kidney parenchyma, any lesion which is sufficient to influence its functional capacity would also and, perhaps, definitely reveal itself in a diminished ability to perform the synthesis. Indeed, this consideration forms the major premise of the argument which soon after Bunge and Schmiedeberg's discovery stimulated the investigation of the hippuric acid synthesis under pathologic conditions by Jaarveld and Stokvis,[8] Weyl and Anrep,[9] and Kronecker.[10] These researches have helped to establish the main contention that the ability to synthesize hippuric acid suffers greatly in the human subject whose kidney parenchyma is diseased.

Recently Violle [11] adopted the method for clinical purposes Realizing that quantitative knowledge of hippuric acid synthesis would throw important light on the physiologic condition of the renal organ, we decided to study this matter further in our hospital patients with primary or secondary kidney affections.

Where Is the Hippuric Acid Synthesized?—As was already pointed out, the quantitative study of hippuric acid excretion under pathologic conditions presupposes that the synthesis takes place in the kidney. It is immaterial if other organs or tissues are likewise potential seats of hippuric acid formation, but if these do contribute appreciably to this synthesis, then obviously there would be little justification for applying the test to estimate the renal function. In 1911, Friedmann and Tachau,[12] perfusing rabbit livers, found that on the addition of benzoic acid, the perfusion blood contained hippuric acid. They advanced the view that in the herbiverous animal, at any rate, the liver partakes in the synthesis. Their method of analysis, however, is quite involved and by no means quantitative (Die beschriebene Method ist keine quantitative). They found that only a limited synthesis occurs, and,

7. Bunge, G., and Schmiedeberg, O.: Ueber die Bildung der Hippursäure, Arch. exper. Pathol. u. Pharmakol. **6**:233, 1876.

8. Jaarveld, G. J., and Stokvis, B. J.: Ueber den Einfluss von Nierenaffectionen auf die Bildung von Hippursäure, Arch. exper. Pathol. u. Pharmakol. **10**:268, 1879.

9. Weyl, T., and Anrep, B.: Ueber die Ausscheidung der Hippursäure und Benzoesäure während des Fiebers, Ztschr. f. physiol. Chem. **4**:169, 1880.

10. Kronecker, F.: Ueber die Hippursäurebildung beim Menschen in Krankheiten, Arch. exper. Pathol. u. Pharmakol. **16**:344, 1883.

11. Violle, P. L.: Recherches sur "l'epreuve de la synthese hippurique" comme moyen d'exploration des fonctions rénales, Ann. de méd. **9**:330, 1921.

12. Friedmann, E., and Tachau, H.: Ueber die Bildung des Glykokolls im Tierkörper. I. Synthese der Hippursäure in der Kaninchenleber, Biochem. Ztschr. **35**:88, 1911.

a very significant finding, that the addition of glycocol to the perfusion blood did not increase the hippuric acid output. In view of this fact, and also because their perfusion experiments with kidneys failed to yield any hippuric acid, the results of Friedmann and Tachau do not seem to us to establish a prima facie case for the hypothesis that the liver participates to an important degree in the synthesis. Of course, these authors, having recognized the convincing force of Bunge and Schmiedeberg's experiments, suggested that a fundamental difference exists between herbiverous and carniverous animals as far as hippuric acid synthesis is concerned. Kingsbury and Bell,[13] however, found relatively large amounts of hippuric acid in the blood and liver of nephrectomized dogs following an injection of sodium benzoate and glycocol. These experiments seemed to break down the demarcation between herbiverous and carniverous animals which Friedmann and Tachau's studies suggested, and to reinforce the hypothesis that hippuric acid synthesis is a generalized function of the organism. It must not be overlooked, however, that the living organism possesses great compensatory ability. Kingsbury and Bell's experiments on dogs with both kidneys removed really prove nothing beyond the fact that in a nephrectomized animal the liver may assume vicariously the function of hippuric acid synthesis. It does not prove that in the intact animal, even when the kidney is diseased, the same thing happens. Lackner, Levinson and Morse,[14] following Kingsbury's lead, studied the effect of liver injury on the hippuric acid synthesis in two dogs. The liver was injured by poisoning with hydrazine sulphate injected subcutaneously. This caused fatty degeneration of the liver but had no effect on the kidneys. A perusal of their data fails to convey clearly the idea of a marked participation of the liver in the hippuric acid synthesis. On the contrary, the extensive liver injury which they produced may be responsible for the failure in some preliminary steps in this process involving the formation of glycocol, a step in which the liver doubtless plays a leading rôle. At any rate, the amino-acid elimination after the hydrazine injection does decrease, as is shown by their own studies. Furthermore, we do not know how much of the benzoic acid administered left the organism without being conjugated with glycocol.

Lewis and Karr [15] have shown that hippuric acid synthesis is associated with a marked diminution in uric acid excretion. While the exact relationship between the two phenomena is not clearly understood, the

13. Kingsbury, F. B., and Bell, E. T.: The Synthesis of Hippuric Acid in Nephrectomized Dogs, J. Biol. Chem. **21**:297, 1915.

14. Lackner, E.; Levinson, A., and Morse, W.: The Rôle of the Liver in Hippuric Acid Synthesis, Biochem. J. **12**:184, 1918.

15. Lewis, H. B., and Karr, W. G.: The Synthesis of Hippuric Acid in the Animal Organism. III. The Excretion of Uric Acid in Man After Ingestion of Sodium Benzoate, J. Biol. Chem. **25**:13, 1916.

observation is nevertheless very important as it indicates that corrolary phenomena in the liver and kidney occur during the synthesis.

The recent extensive investigation of Delprat and Whipple,[16] who produced varying degrees of liver injury in dogs by the use of chloroform, bear out this point of view. These investigators found no change in the hippuric acid synthesis, except when the injury to the liver was very severe. On the other hand, Kingsbury and Bell's [17] investigation on rabbits which were made nephritic by injecting racemic tartaric acid revealed a considerable reduction in the per cent. of synthesized hippuric acid besides the great increase in the free benzoic acid excretion following the injury.

Considering all the evidence, the conclusion cannot be escaped that the kidney is probably the place of hippuric acid synthesis. This does not exclude the possibility that under exceptional and wholly unnatural circumstances the liver, or some other organ, may not vicariously assume this function as well. Those, however, who are inclined more favorably to the hypothesis that the hippuric acid synthesis is normally a generalized function must still produce acceptable evidence for their view.

Kingsbury and Swanson,[18] in their recent study of the synthesis and elimination of hippuric acid, came to the conclusion that "in nephritis hippuric acid is synthesized completely, and as far as can be learned, at practically the same rate as in normal individuals." We have no criticism to offer of their experiments, except to point out that in our opinion their assumption that the free benzoic acid output is negligible is not entirely warranted. Inasmuch as they omitted the free benzoic acid from their determinations, this conclusion could more properly be interpreted as referring to the total benzoic excretion rather than to the hippuric acid synthesis. The results of our experiments with nephritic and cardiorenal patients, which we present in this paper, do not bear out their conclusion, as will be seen subsequently.

METHODS OF ANALYTICAL AND EXPERIMENTAL PROCEDURE

The hippuric acid output in the urine was determined according to the method recommended by Kingsbury and Swanson.[19] The hippuric acid, of course, is formed through the conjugation of benzoic with

16. Delprat, G. D., and Whipple, G. H.: Liver Function. Benzoate Administration and Hippuric Acid Synthesis, J. Biol. Chem. **49**:229, 1921.

17. Kingsbury, F. B., and Bell, E. T.: The Synthesis of Hippuric Acid in Experimental Nephritis in the Rabbit, J. Biol. Chem. **20**:73, 1915.

18. Kingsbury, F. B., and Swanson, W. W.: The Synthesis and Elimination of Hippuric Acid in Nephritis: A New Renal Function Test, Arch. Int. Med. **28**:220 (Aug.) 1921.

19. Kingsbury, F. B., and Swanson, W. W.: A Rapid Method for the Determination of Hippuric Acid in Urine, J. Biol. Chem. **48**:13, 1921.

amino-acetic acid (glycocol), and the estimation of the hippuric acid depends on reactions involving, first, the breaking up of this combination and, second, measuring the amount of benzoic acid thus set free. The benzoic acid is then extracted with chloroform and titrated against a standard solution of sodium alcoholate. Inasmuch as benzoic acid which may already have been present in the urine, before the hydrolysis of hippuric, would likewise be extracted in the process, it is obvious that a correction must be made for the free benzoic acid or its salts appearing in the urine. Under some conditions the correction may be entirely negligible having no effect on the calculation of the amount of hippuric acid. Then, again, as in our experience at any rate, this correction may assume considerable importance. Therefore, in all our analyses we made separate determinations of the free benzoic acid even when we had reason to expect that this would be a neglible quantity. Our determinations were invariably on duplicate samples for both the total benzoic and the free benzoic acid in the urine.

The pathologic urines with which we worked all contained albumen in greater or smaller amounts, and it was necessary as a first step in the analysis to free the urines from this, as otherwise entirely erroneous results might have been obtained. For the purpose of deproteinizing, sodium hydroxid was added until the strongly acid urine reacted just faintly acid to litmus. Then 0.5 gm. tannic acid was added to every 100 c.c. of urine. A floculent precipitate was formed in the presence of albumen which was filtered off after allowing the mixture to stand for a few minutes. Control experiments with normal urines of which one portion was treated in a similar manner with the tannic acid while the other was analyzed without such preliminary treatment, showed that this deproteinizing treatment had no effect on the results of the benzoic acid determination. The precipitate was filtered off and the filtrates were tested to ascertain that the deproteinization was complete.

Of the deproteinized urines 100 c.c. samples were immediately measured out into separatory funnels and saturated with ammonium sulphate. The mixture was then strongly acidified by the addition of 1 c.c. of concentrated nitric acid and extracted with four portions of washed freshly distilled chloroform (50, 35, 25 and 25 c.c., respectively). Raiziss and Dubin [20] recommend the use of toluol for this extraction, but Delprat and Whipple [16] have found that chloroform can be used with as good results. The formation of emulsions, which seems to be the chief reason for employing toluol instead of chloroform, did not cause us any trouble in the analyses, except in one instance, when the determination was lost on that account.

20. Raiziss, G. W., and Dubin, H.: On the Estimation of Benzoic Acid in the Urine, J. Biol. Chem. **20**:125, 1915.

For determining the total benzoic acid, 50 c.c. portions of urine were usually taken unless much benzoic was expected, in which case 25 c.c. (diluted with water to 50 c.c.) was taken instead. The urine, mixed with 7.5 gm. sodium hydroxid and 0.5 gm. magnesium oxid was boiled down in a Kjeldahl flask to half this volume. One c.c. of saturated potassium permanganate was added and the contents of the flask well mixed by twirling. After cooling, the flasks were clamped in an upright position. A Hopkins condenser was inserted in the neck, through which a rapid stream of water has been kept flowing. Thirty c.c. of nitric acid was then poured cautiously into the flask and the contents digested for forty-five minutes over a gentle flame. The mixture became a clear, sparkling, yellow liquid which after cooling was transferred to a separatory funnel, saturated with ammonium sulphate and extracted with four portions of chloroform (50, 35, 25 and 25 c.c., respectively), as in the case of the free benzoic acid determination. The combined chloroform extracts were now washed in a clean separatory funnel with Folin and Flander's acidulated sodium chlorid solution (saturated) and the chloroform drawn off through a filter into a clean Erlenmeyer flask. The combined and thoroughly washed extracts were now titrated with tenth normal sodium alcoholate, using phenolphthalein as an indicator.

The chloroform employed in our analyses was invariably purified before being used. For this purpose it was first washed with water and distilled, then washed again with saturated salt solution and redistilled. From time to time we checked up the quality of our chloroform by titrating an amount equivalent to that used for the extraction, but the addition of a single drop of the sodium alcoholate was sufficient to impart to the chloroform a deep red color.

The sodium alcoholate was prepared by weighing out the theoretic amount of metallic sodium and dissolving in absolute alcohol. This we prepared from purchased absolute alcohol, by boiling under a reflux condenser with calcium oxid and then redistilling it. The strength of the standard alcoholate was set by titrating measured quantities of an exact tenth normal benzoic acid prepared in toluol.

A word with regard to the procedure followed in the extraction with chloroform may not be amiss. The liquid to be extracted was shaken with the chloroform three times in succession, for periods of one minute, the two liquids being allowed to separate between successive shakings. We carried out determinations with known amounts of benzoic acid and satisfied ourselves that we recovered by this procedure the entire amount. To insure complete uniformity in the analyses the above routine was strictly adhered to in all determinations.

It is also, perhaps, well to mention that we made blank and check determinations to be sure that the analytic process as carried out by us was reliable in its results.

The patients on whom the hippuric synthesis test was performed were given a diet poor in benzoic acid, no fruit and only very little vegetables being allowed. They were also given no medication, not even alkali, during the entire period of the test. In later experiments, in order to limit the benzoic acid elimination as much as possible, a diet consisting exclusively of milk and toast was prescribed, starting at least one day before the test. In the earlier experiments we collected three twenty-four hour urines: one, as a preliminary urine, to find out the benzoic and hippuric acid output of the patient; the second urine (from twenty-four to forty-eight hours) followed the administration of a definite quantity either of sodium benzoate or benzoic acid; and a third urine (from forty-eight to seventy-two hours), to note the after-effect. The drug, either as benzoic acid or as the sodium salt, was administered exactly at the moment when the second urine sample was started. Inasmuch as the third urine proved of no particular importance in the test of the hippuric acid synthesis, it was omitted altogether in later experiments. Furthermore, to still further shorten the period covered by the test, a preliminary urine sample was taken for six hours (usually from 6 a. m. till noon). The patient received the substance at 12 noon, when the second urine sample was opened. It was closed at 6 p. m. giving a six hour urine following the benzoic acid ingestion. A third sample was then collected from 6 p. m. until noon the next day. The two last urines, therefore, gave the total benzoic and hippuric acid output for twenty-four hours after a known amount of benzoic acid was administered.

The urines were preserved with thymol and kept in a cool place. As soon as a sample was closed it was analyzed. To find out whether any hydrolysis of hippuric acid occurred spontaneously during the interval of time elapsing between the opening of the urine sample and the actual analysis, we examined aliquot portions of urine preserved in the usual manner immediately after being voided and at various times subsequently just as happened with our experimental urines. The same quantity of the urine was analyzed for free benzoic acid, and the same routine procedure was followed but we failed to find any change in the titration values within the limits of time occupied by our experiments. It is well to remember that the urines were always strongly acid. We are satisfied, therefore, that the changes in free benzoic acid elimination which we observed under the circumstances of our tests were not due to the setting free of benzoic acid from its combination with glycocol (i. e., the decomposition of hippuric acid) but must be regarded as being actually excreted by the kidneys.

DISCUSSION OF CASES

Before discussing the hippuric acid synthesis and the excretion of benzoic acid in a number of hospital patients, it is well to detail our findings with normal persons. We shall, therefore, report a few tests performed on perfectly healthy subjects.

In the accompanying graphs free benzoic acid is represented by the unshaded portion. The cross striated blocks represent the total benzoic acid while the longitudinally striated ones represent the hippuric acid. The arrows point to the theoretical level of hippuric and benzoic acid excretions.

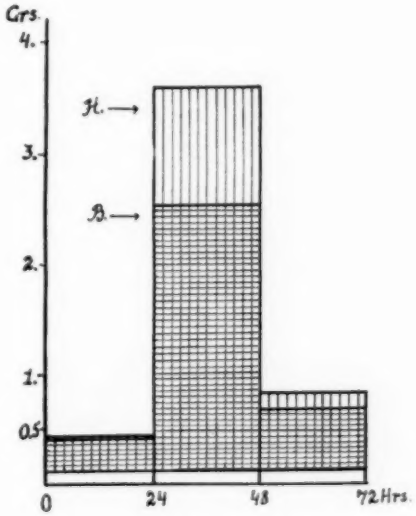

Fig. 1.—Case 1.

CASE 1.—H. M. J. A twenty-four hour urine sample was collected before the subject took 2.4 gm. sodium benzoate dissolved in water. This preliminary urine contained 0.409 gm. of total benzoic acid. Inasmuch as 0.117 gm. was in free condition, the remaining benzoic acid was bound to form 0.428 gm. hippuric acid. The twenty-four hour urine following the ingestion of 2.4 gm. sodium benzoate (=2.033 gm. benzoic acid) contained 2.556 gm. benzoic acid. The free benzoic acid was practically unchanged (0.122 gm.) and the hippuric acid output was 3.572 gm. When the correction for the hippuric and benzoic acid content of the daily urine is made, the subject eliminated 5 per cent. more than the theoretically expected amount of both. During the third twenty-four hour period the urine contained 0.667 gm. benzoic acid. The benzoic acid in free condition was still practically the same as on the previous two days (0.111 gm.), and the hippuric acid output was 0.815 gm.

CASE 2.—S. M. The preliminary twenty-four hour urine of this subject contained 1.036 gm. benzoic acid and of this amount 0.173 gm. was not conjugated, the hippuric acid output being thus 1.267 gm. The subject took 2.4 gm. sodium benzoate in water and in the next twenty-four hours the benzoic acid

content of the urine reached 3.202 gm. The free benzoic acid increased to 0.307 gm., the remainder being conjugated in the form of 4.248 gm. hippuric acid. The urine collected for the third twenty-four hour period contained 1.172 gm. benzoic acid. The free benzoic acid elimination diminished again to 0.261 gm. leaving the remainder conjugated in 1.336 gm. of hippuric acid. Making the proper corrections, the subject synthesized 100 per cent. of the theoretically expected amount of hippuric acid. The benzoic acid excretion during this twenty-four hour period following the benzoic administration was actually 4 per cent. over and above the theoretic amount, the excess being in the form of free benzoic acid.

In either case with the normal subject, the benzoate ingestion not only resulted in a complete synthesis of benzoic to hippuric acid but

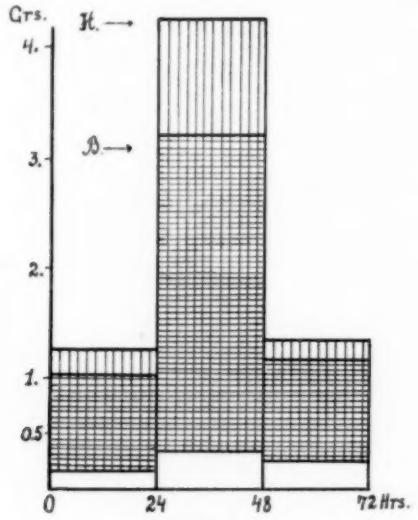

Fig. 2.—Case 2.

the kidney was apparently stimulated to greater activity. This stimulation of the kidney is seen not only in the excess over the theoretic amount which was recovered from the urines passed within twenty-four hours after the benzoate administration but also in an increased hippuric acid output forty-eight hours later. This last fact gains significance by contrast with what is usually found under pathologic conditions, as will be pointed out subsequently.

Case 3.—S. M. Tests were also made in which benzoic acid was given in place of the sodium benzoate. The results are not essentially different from those presented in the above experiments but we shall report one example. The subject was on a diet poor in benzoic acid (fruit and vegetable free). The preliminary urine for six hours contained 0.299 gm. benzoic acid and 0.425 gm. hippuric, the free benzoic acid being practically negligible (0.009 gm.). Two

grams benzoic acid was then taken in gelatin capsules and the urine analyzed every three hours during the day. In the first three hours 82 per cent. of the theoretic amount of hippuric acid appeared in the urine. By the end of six hours virtually 98 per cent. of the benzoic acid was already eliminated and 96 per cent. of the expected synthesis in the hippuric acid occurred.

This corresponds to Lewis' findings where, with much larger doses (from 6 to 10 gm.) of sodium benzoate, about 90 per cent. was recovered in the form of hippuric acid in the five or six hour urine.[21] In the eighteen hours completing the twenty-four hours' sample, little further change took place, but the total benzoic acid recovered within the twenty-four hours was 99 per cent. of the theoretical.

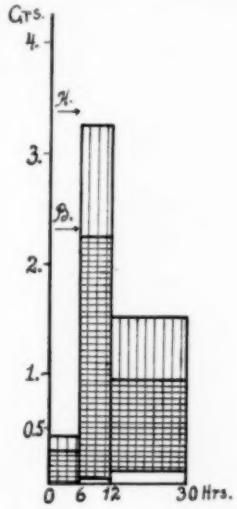

Fig. 3.—Case 3.

We will now consider the hippuric acid synthesis and benzoic acid excretion in a number of pathologic cases.

Case 4.—L. E. P., female, aged 37, came to one of us (G. P. P.) for advice Sept. 30, 1921.

History.—Six weeks ago she first noticed some puffiness about the eyes and hands. In the morning the swelling became more marked. Her legs are now swollen. She feels tired and has an occasional headache. She passes a small amount of urine. No nocturia is present.

Past Illness.—Influenza in 1918, when she remained in bed four weeks. She was in a hospital two weeks in 1919 for "stomach trouble." In May, 1921, she had tonsillitis with a complicating peritonsillar abscess. Measles, pertussis, and diphtheria during childhood.

21. Lewis, H. B.: The Synthesis and Rate of Elimination of Hippuric Acid After Benzoate Ingestion in Man, J. Biol. Chem. **18**:225, 1914.

Physical Examination.—Temperature, 98.6 F.; pulse, 70; respiration, 20. The legs are edematous and there is puffiness about the eyes in the morning. Eye-grounds negative; pupils equal and active; tonsils hypertrophied; many filled teeth; roentgenogram of teeth revealed fourteen peri-apical abscesses. The lungs are quite normal. The heart sounds are normal. The heart is normal in size and the rhythm is regular. The blood vessels are not thickened. Blood pressure, 135/80. The abdomen is negative. The reflexes are normal.

Laboratory Examination.—Blood: Wassermann test negative. Red blood cells, 4,210,000; white blood cells, 6,900; hemoglobin, 80 per cent.; 100 c.c. of blood contained 91 mg. sugar, 48 mg. nonprotein nitrogen and 1.8 mg. uric acid.

Urine: Acid, cloudy, specific gravity, 1.024; albumin, four plus; no sugar. Microscopic examination: granular and hyaline casts, white blood cells and an occasional red blood cell.

Diagnosis.—Subacute diffuse nephritis.

Tests of Kidney Function: Phenolsulphonephthalein output in two hours and ten minutes, 45 per cent.

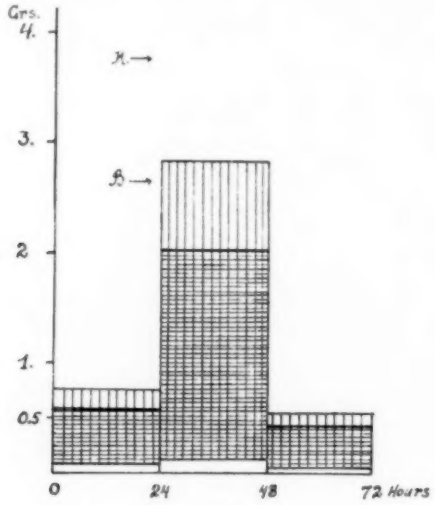

Fig. 4.—Case 4.

Hippuric Acid Test: The preliminary twenty-four hour urine contained 0.604 gm. benzoic acid of which 0.080 gm. was free and the remainder conjugated in the form of 0.758 gm. hippuric acid. The patient received 2.4 gm. sodium benzoate and following the administration another twenty-four hour urine was collected. This urine contained 2.022 gm. benzoic acid of which 0.120 gm. was free. The remaining portion was conjugated to form 2.822 gm. hippuric acid. Since the theoretically expected amount of total benzoic acid was 2.634 gm. only 77 per cent. was recovered. Of the expected 3.736 gm. hippuric acid only 76 per cent. was synthesized in twenty-four hours. A third twenty-four hour sample contained 0.428 gm. total benzoic acid with 0.054 gm. in the free state. It contained, therefore, 0.548 gm. hippuric acid.

Case 5.—S. S., female, aged 36, admitted to the University Hospital Feb. 9, 1922.

History.—She noticed about a year ago that it was hard to see with the left eye. The dimness of vision increased until two weeks ago a similar process attacked her right eye. She suffers shortness of breath on exertion. The urine is abundant with nocturia two or three times.

Past Illness.—For several months in 1906 she suffered from swollen ankles. This was usually worse in the evening. She had measles and diphtheria during childhood.

Physical Examination.—Temperature, 99 F.; pulse, 80; respiration, 20. Patient is rather heavy with slight edema of the ankles. She has "albuminuric retinitis" in both eyes, more marked on the left side; pupils equal and active; tonsils congested and hypertrophied; pyorrhea; pus can be expressed from lower incisors and there are four teeth with large cavities. The lungs are quite normal; the heart is moderately enlarged and the aortic second is accentuated. The blood vessels are somewhat thickened. Blood pressure, 220/170. The liver can be felt one finger breadth below the costal margin. The reflexes are normal.

Laboratory Examination.—Blood: Wassermann test negative. Red blood cells, 4,147,000; white blood cells, 8,400; hemoglobin, 85 per cent.; 100 c.c. of blood contained 120 mg. sugar, 65 mg. nonprotein nitrogen, and 4.5 mg. uric acid.

Urine: Acid; specific gravity, 1.010; albumin, three plus; no sugar. Microscopic examination: hyaline casts.

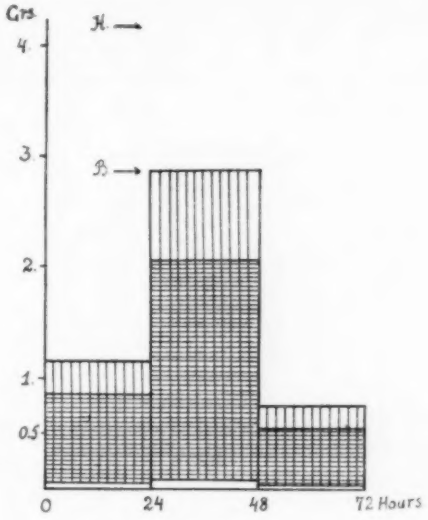

Fig. 5.—Case 5.

Diagnosis.—Cardiovascular renal disease.

Tests of Kidney Function: Phenolsulphonephthalein output in two hours ten minutes, 15 per cent.

Hippuric Acid Test: The preliminary urine sample for twenty-four hours contained a total of 0.848 gm. benzoic acid of which 0.058 gm. were in free condition; the hippuric acid content was, therefore, 1.159 gm. The patient received 2.4 gm. sodium benzoate and a twenty-four hour urine following the ingestion contained a total of 2.046 gm. benzoic acid with 0.082 gm. of the free acid, the remaining fraction conjugated to form 2.881 gm. hippuric acid. Comparing these quantities with those theoretically expected, only 59 per cent. of the total benzoic and 58 per cent. of the hippuric acid were recovered in the twenty-four hours. During the third twenty-four hour period the patient eliminated a total of 0.545 gm. benzoic acid. The free benzoic acid had diminished to 0.038 gm., the rest being conjugated to form 0.744 gm. of hippuric acid.

Case 6.—F. K. K., male, aged 53, admitted to the University Hospital Feb. 22, 1922.

History.—Patient returns to hospital on account of edema affecting the lower extremities, which is worse in the evening. Dyspnea and precordial pain. He was admitted to the hospital June 9, 1921, for six weeks and again Sept. 6, 1921, for three months, both times for cardiac decompensation.

Past Illness.—At 18 he had acute articular rheumatism; denies having had any other diseases.

Physical Examination.—The patient is poorly nourished and not well developed. Eyegrounds: small retinal hemorrhages in both eyes; pupils equal and active; tonsils small; teeth in good condition. The lungs show evidence of congestion at both bases. The heart is markedly enlarged, the rhythm is irregular and there is a systolic murmur at the apex. The blood vessels are sclerotic. Blood pressure, 205/125. The liver is enlarger two fingers breadth below the costal margin. There is edema about the ankles extending to the knees.

Laboratory Examination.—Blood: Wassermann test, negative. Red blood cells, 4,000,000; white blood cells, 7,200; hemoglobin, 80 per cent.; 100 c.c. blood contained 100 mg. sugar, 61 mg. nonprotein nitrogen and 4.5 mg. uric acid:

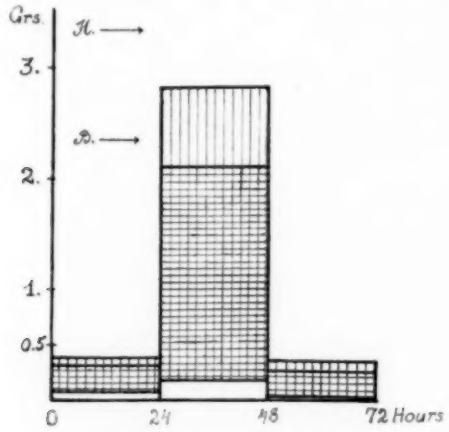

Fig. 6.—Case 6; first test.

Urine: Acid; specific gravity, 1.015; albumin, one plus; no sugar. Microscopic examination: hyaline and granular casts.

Diagnosis.—Cardiovascular renal disease.

Tests of Kidney Function: Phenolsulphonephthalein output in two hours ten minutes, 40 per cent.

Hippuric Acid Test: This has been repeated three times for this patient. First test, March 15 to 18. The preliminary twenty-four hour urine contained 0.322 gm. benzoic acid, of which 0.059 gm. was free. The hippuric acid was, therefore, 0.387 gm. The patient was given 2.4 gm. sodium benzoate, and a second twenty-four hour urine was collected. This contained 2.115 gm. benzoic acid with 0.176 gm. as free benzoic. The hippuric acid was thus 2.845 gm. Only 88 per cent. of the theoretically expected total benzoic acid and 83 per cent. of the hippuric acid was recovered. In the next twenty-four hours the urine contained 0.273 gm. of total benzoic acid, and as there was present 0.027 gm. of the free acid, 0.362 gm. were eliminated in the form of hippuric acid.

Second test, March 21-23. The test was performed as before, except that 2 gm. benzoic acid put up in gelatin capsules was administered instead of sodium benzoate. The preliminary twenty-four hour urine is very similar to that of the first test. It contained 0.287 gm. benzoic acid with 0.031 gm. in the free state and the rest conjugated to form 0.376 gm. hippuric acid. In the twenty-four hours following the ingestion of the benzoic acid 1.830 gm. of total benzoic acid was excreted. Of this 0.332 gm. was free acid and the rest was conjugated in 2.197 gm. hippuric acid. This time we recovered, therefore, only 77 per cent. of the benzoic acid and 62 per cent. of the theoretically expected hippuric acid. During the third twenty-four hour period the total benzoic acid in the urine was 0.381 gm. and the free benzoic acid returned to the level of the preliminary urine (0.052 gm.). The hippuric acid was 0.483 gm.

Third Test: About a month later we applied the test once more in a somewhat modified form. The patient's diet was limited to milk and toast. Unfortunately, the patient was unwilling to cooperate and could not be persuaded

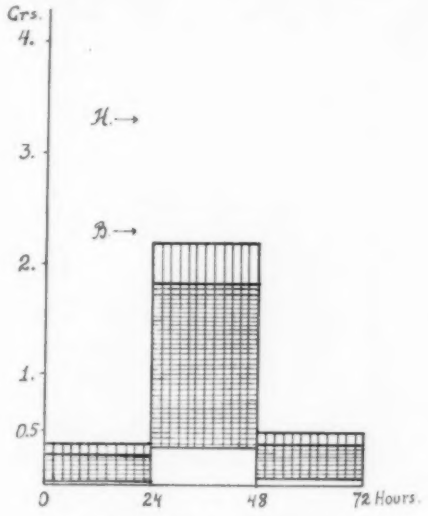

Fig. 7.—Case 6; second test.

to take enough liquid, either milk or water. In consequence, his urinary output diminished very considerably. Although we do not attach much significance to this test, we are recording it because of the general interest it has with regard to the question of hippuric acid synthesis.

After the patient had been on milk and toast for one day, a six hour urine sample was collected and 2 gm. benzoic acid in capsules was given to the patient. There was only 40 c.c. of the preliminary urine and this contained 0.051 gm. benzoic acid, or 0.076 gm. hippuric acid. A second six hour urine sample was obtained after the patient had taken 2 gm. benzoic acid. This second sample (65 c.c.) contained 0.357 gm. of total benzoic acid. As there was 0.059 gm. of free acid, he eliminated 0.478 gm. hippuric acid. We find, therefore, that in six hours the patient excreted only 15 and 14 per cent., respectively, of the theoretically expected benzoic and hippuric acid. A third urine (315 c.c.) was collected for eighteen hours (completing the twenty-four hour sample following the benzoic acid ingestion) and this contained 0.939 gm. benzoic acid. Since

0.067 gm. was free benzoic the rest made up 1.280 gm. hippuric acid. The total elimination for the twenty-four hour period was, therefore, 55 per cent. of the benzoic acid administered and 50 per cent. of the expected hippuric synthesis.

The much reduced output of both hippuric and benzoic acid noted in this last test we ascribe to the fact that the patient's urinary secretion during this period was very scanty. In fact, when the results of the three tests performed for this patient are compared, it is obvious that the hippuric acid synthesis follows closely the total urinary excretion. It would be difficult to understand these coincident changes in kidney activity if the hippuric acid synthesis was not a kidney function. The third test also emphasizes the necessity of providing an ample amount of fluid in order that the urine output should be sufficient and the

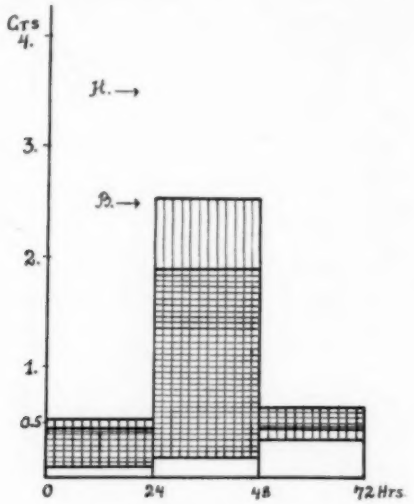

Fig. 8.—Case 7; first test.

hippuric acid synthesis should not be interfered with on that account. It must further be pointed out that in patients whose urine output is naturally limited the test may lead to erroneous conclusions.

CASE 7.—H. R., male, aged 20, admitted to University Hospital, Jan. 19, 1922.

History.—One month ago patient developed a general anasarca. The swelling especially in the mornings, was most marked in the legs and face. Complains of shortness of breath. There is nocturia from three to four times.

Past Illness.—The patient was in the hospital two and one-half years ago for acute nephritis following tonsillitis. He remained in the hospital for a while and has been up and about since, working most of the time, until the present illness. He has had mumps, measles and frequent attacks of tonsillitis.

Physical Examination.—Patient presents the characteristic pasty appearance. Eyegrounds negative; pupils equal and active; tonsils have been removed; pil-

lars are congested; teeth are in good condition. The lungs are negative. The heart is slightly enlarged, with an accentuated second aortic sound. Blood pressure, 180/110. The abdomen is negative. The reflexes are sluggish. Edema about the ankles.

Laboratory Examination. — Blood: Wassermann test negative. Red blood cells, 3,136,000; white blood cells, 14,400; hemoglobin, 60 per cent.; 100 c.c. of blood contained 98 mg. sugar, 117 mg. nonprotein nitrogen, and 6.5 mg. uric acid.

Urine: Alkaline;[22] specific gravity, 1.013; albumin, four plus; no sugar.

Microscopic Examination: Numerous granular casts, red cells.

Diagnosis.—Chronic diffused nephritis.

Tests of Kidney Function: Phenolsulphonephthalein output in two hours and ten minutes, 10 per cent.

Hippuric Acid Test: The preliminary twenty-four hour urine contained 0.448 gm. of total benzoic acid. As there was 0.089 gm. of free benzoic acid the remainder was bound in 0.527 gm. hippuric acid. Following the intake of 2, 4 gm. sodium benzoate, the twenty-four hour urine contained 1.879 gm. benzoic acid with 0.165 gm. in the form of acid. The hippuric acid output was, therefore, 2.515 gm. Introducing the necessary corrections,

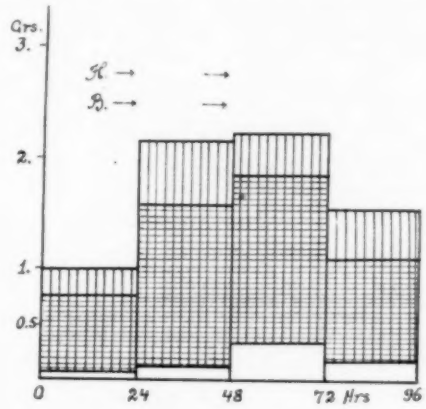

Fig. 9.—Case 7; second test.

we find that in the twenty-four hours 76 per cent. of the benzoic acid and 72 per cent. of the theoretically expected hippuric acid was recovered. In the next period of twenty-four hours the patient eliminated 0.634 gm. benzoic acid. The free benzoic acid in the urine showed a further increase to 0.333 gm. The hippuric acid output during the third twenty-four hour period was, therefore, 0.441 gm. At a later time we repeated the test, administering 1.2 gm. sodium benzoate on two consecutive days instead of the single dose of 2.4 gm. The results of this test (Fig. 9) are essentially the same as that of the previous test.

Case 8.—C. W., male, aged 72, was admitted to University Hospital March 21, 1922.

History.— Patient has had precordial pain and shortness of breath at intervals for several years. In the past five months dizziness has become troublesome. There has been nocturia for three years.

22. During the hippuric acid tests alkalinization of the patient was discontinued and the urines were invariably strongly acid.

Past Illness.—Pneumonia in adult life.

Physical Examination.—Patient is well nourished. Eyegrounds are negative; pupils equal and active; tonsils negative; teeth all extracted. Lungs show evidences of slight congestion at the bases. The heart is slightly enlarged; sounds distinct; no murmurs. Blood pressure, 170/85. Abdomen is negative. Extremities normal.

Laboratory Examination.—Blood: Wassermann test negative. Red blood cells, 5,280,000; white blood cells, 6,600; hemoglobin, 75 per cent.; 100 c.c. blood contained 110 mg. sugar, 48 mg. nonprotein nitrogen.

Urine: Acid; specific gravity, 1.020; albumin, one plus; no sugar. Microscopic examination: hyaline casts.

Diagnosis.—Cardiovascular renal disease.

Tests of Kidney Function: Phenolsulphonephthalein output in two hours and ten minutes, 50 per cent.

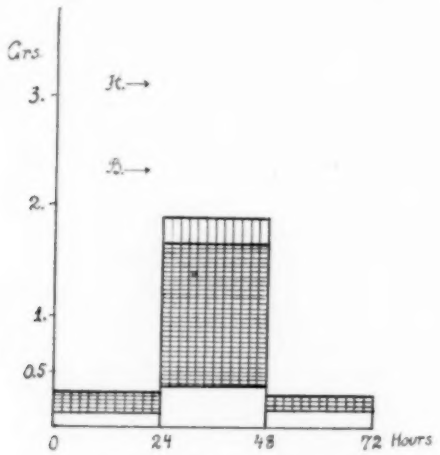

Fig. 10.—Case 8; first test.

Hippuric Acid Test: The test has been repeated several times with this patient. First Test: The preliminary twenty-four hour urine sample contained 0.311 gm. benzoic acid, with 0.098 gm. in a free state. The remainder formed 0.313 gm. of hippuric acid. Following the ingestion of 2.4 gm. of sodium benzoate, the twenty-four hour urine contained 1.665 gm. benzoic with 0.375 gm. as free acid. The hippuric acid output corresponding to the remainder of the benzoic acid was 1.892 gm. When the proper correction for the normal elimination is made, 67 per cent. of the ingested benzoic acid was recovered in the twenty-four hours and 53 per cent. of the theoretic amount of hippuric acid. The third twenty-four hour urine is much lower in benzoic acid content than the preliminary—only 0.290 gm. of total benzoic acid being present. The hippuric acid excretion was 0.200 gm.

Second Test: This test was applied five days later, the only modification being that 2 gm. benzoic acid in gelatin capsules was administered this time. The preliminary twenty-four hour urine contained 0.544 gm. of total benzoic acid. The free benzoic acid in the urine was still high, 0.171 gm., so that 0.547 gm. of hippuric acid was eliminated in the twenty-four hours. Following the ingestion of the 2 gm. of the benzoic acid, the twenty-four hour urine

contained 2.272 gm. benzoic acid. As was also the case in the first test, the free benzoic acid increased to 0.325 gm. The patient excreted, therefore, 2.857 gm. hippuric acid. Making the necessary corrections, we find that this time we recovered 87 per cent. of the benzoic acid and 79 per cent. of the hippuric acid theoretically expected. In the subsequent twenty-four hours there was only 0.420 gm. total benzoic acid. The free benzoic acid determination was lost and the hippuric acid output could not, therefore, be calculated accurately, but it is evident that it was appreciably lower than in the preliminary twenty-four hours.

Third Test: In view of the fact that this patient showed persistently a relatively high free benzoic acid excretion, we put him exclusively on a milk and toast diet. A six hour preliminary urine sample was obtained in which the free benzoic acid was reduced to a practically negligible level. The total

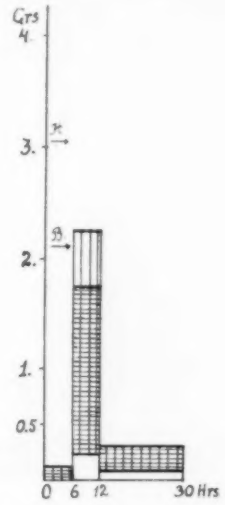

Fig. 11.—Case 8; third test.

benzoic acid for these six hours was 0.088 gm. and the hippuric acid was 0.116 gm. The patient was given 2 gm. benzoic acid in capsules. The urine for the next six hours contained 1.757 gm. total benzoic acid and the free benzoic acid increased to 0.224 gm. The hippuric acid output was 2.248 gm. In six hours following the ingestion of benzoic acid, 84 per cent. was recovered in the urine, of which 73 per cent. was in the form of hippuric acid. The urine for the next eighteen hours contained 0.281 gm. benzoic acid (with 0.085 gm. in the free state) and 0.288 gm. hippuric acid. When the total elimination for twenty-four hours following the benzoic acid administration is considered, we find that during the entire period 84 per cent. of benzoic and 71 per cent. of hippuric acid have been recovered. In other words, there has been practically no change from what had happened in the first six hours.

Case 9.—A. W., male, aged 32, was admitted to the University Hospital March 6, 1922.

History.—Three years ago patient was refused life insurance on account of kidney trouble, albumin in the urine, and high blood pressure.

Past Illness.—Measles and chickenpox during childhood and influenza in 1918.

Physical Examination.—Patient is well nourished and well developed. Eyegrounds are negative; pupils equal and accurate; tonsils buried; teeth are in good condition. Lungs are negative. The heart very slightly enlarged. Blood pressure, 175/110. Abdomen negative. Reflexes active.

Laboratory Examination.—Blood: Wassermann negative. Red blood cells, 3,900,000; white blood cells, 6,200; hemoglobin, 74 per cent.; 100 c.c. contained 98 mg. sugar, 74 mg. nonprotein nitrogen, 5.4 mg. uric acid.[23]

Urine: Acid; specific gravity, 1.013; albumin, two plus; no sugar. Microscopic examination: hyaline and granular casts.

Diagnosis.—Chronic diffuse nephritis.

Tests of Kidney Function: Phenolsulphonephthalein output in two hours and ten minutes, 15 per cent.

Hippuric Acid Test: A preliminary twenty-four hour urine was collected to determine the base line for the benzoic and hippuric acid excretion. The total benzoic acid output was found to be 0.471 gm. Since the free benzoic acid

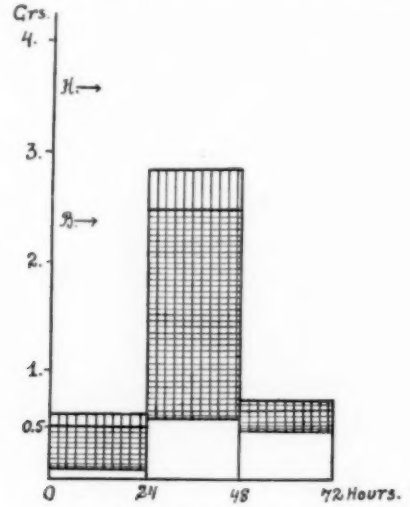

Fig. 12.—Case 9.

was 0.081 gm. there was 0.572 gm. of hippuric acid. The patient received 2.4 gm. sodium benzoate and a twenty-four hour urine was again collected. The total benzoic acid output rose to 2.428 gm. and of this amount 0.534 gm. was in the form of free benzoic acid. The hippuric acid output was, therefore, 2.778 gm. Correcting for the normal excretion, 96 per cent. of the ingested benzoic acid was recovered in twenty-four hours. Owing to the fact that a large amount of the benzoic acid was unconjugated, only 74 per cent. of the theoretically expected hippuric acid was synthesized and excreted. The third twenty-four hour urine presented considerable interest. The total benzoic acid output was relatively high (0.719 gm.) and the free benzoic acid still remained at a very high level (0.467 gm.) so that only 0.459 gm. of hippuric acid were eliminated.

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23. A blood analysis made two and a half months later gave the following results: 150 mg. sugar, 90 mg. nonprotein nitrogen, 3.1 mg. uric acid, and 3.6 mg. creatinin.

When the benzoic and hippuric acid output for the three consecutive days occupied by the test are summed up, we note that 3.618 gm. benzoic acid were recovered. Making the necessary corrections on the basis of the data for the premilinary period and also for the amount administered in the form of 2.4 gm. sodium benzoate, we find a small excess of benzoic acid (0.175 gm. above the theoretically expected amount). When we calculate in a similar manner the hippuric acid, we find that only 83 per cent. of the expected synthesis has taken place. These results are significant, especially as we are dealing in this case with a true nephrosis. The kidney of the nephritic patient is evidently quite capable of excreting benzoic acid and the full amount that could be expected passed through the urine. The matter is entirely different when we consider the kidney's synthetic ability, and even forty-

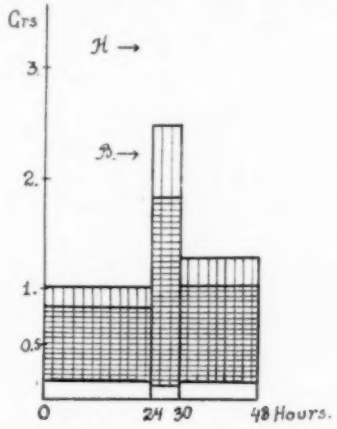

Fig. 13.—Case 10; first test.

eight hours after the administration of sodium benzoate only 83 per cent. of the possible synthesis was accomplished. It is evident, therefore, that the excretion of benzoic acid by the kidney and its synthesis to hippuric acid are either distinct functions or are carried out by different structural parts of the kidney. We shall see other instances in which, unlike the ones discussed previously, a high degree of excretory power goes hand in hand with a relatively low grade of synthetic power. If the synthesis of hippuric acid occurred anywhere else in the body outside the kidney, these results would be difficult to interpret, as there is no evidence of a lesion anywhere except in the kidney.

CASE 10.—J. F. L., male, aged 62, was admitted to the University Hospital April 12, 1922.

History.—For more than ten years the patient has suffered shortness of breath on exertion, frequency of urination, with nocturia. At times he has

had severe asthmatic attacks. Three weeks before admission he was seen by us and at that time there was a general anasarca, especially marked in the abdominal vaults and scrotum.

Past Illness.—Measles, mumps and pertussis during childhood. He had malaria in 1885 and again in 1908.

Physical Examination.—Patient is fairly well developed and well nourished. Eyegrounds are negative; pupils equal and active; tonsils normal; teeth in poor condition. Emphysematous type of chest; hyperresonant throughout; dry râles at the end of expiration. Heart moderately enlarged; systolic murmur at the apex; aortic second accentuated. The arteries are somewhat thickened. Blood pressure, 150/80. Abdomen negative. Reflexes active.

Laboratory Examination.—Blood: Wassermann test negative. Red blood cells, 2,230,000; white blood cells, 7,000; hemoglobin, 50 per cent.; 100 c.c. of blood contained 109 mg. sugar, 56 mg. nonprotein nitrogen and 4.8 mg. uric acid.

Urine: Acid; specific gravity, 1.010; albumin, two plus; no sugar. Microscopic examination: hyaline and granular casts; many white blood cells and a few red blood cells.

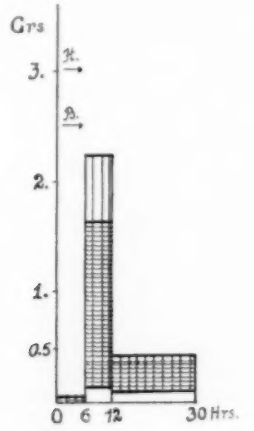

Fig. 14.—Case 10; second test.

Diagnosis.—Cardiovascular renal disease.

Tests of Kidney Function: Phenolsulphonephthalein output in two hours ten minutes, 35 per cent.

Hippuric Acid Test: First test: A preliminary twenty-four hour urine was collected. It contained 0.837 gm. total benzoic acid, with 0.142 gm. in the free state. The hippuric acid was therefore 1.019 gm. The patient ingested 2 gm. benzoic acid put up in gelatin capsules, and a six hour urine sample was taken immediately afterward. This contained 1.819 gm. of total benzoic acid. The free benzoic acid elimination rose to 0.124 gm. in six hours. The hippuric acid output in the same time was 2.488 gm. with proper corrections, therefore, 81 per cent. of the ingested benzoic acid was recovered in six hours, and 76 per cent. of the theoretically expected hippuric acid synthesis. A third urine for eighteen hours contained 1.015 gm. of total benzoic acid, of which 0.143 gm. was in an unconjugated state. The hippuric acid output was 1.280 gm. For the entire twenty-four hour period following the administration of 2 gm. of benzoic acid, 100 per cent. of the complete dose was recovered in the urine and 95 per cent. of the expected hippuric acid. The results of this test are, therefore, comparable to those found in Case 10.

Second Test: Owing to the fact that the free benzoic acid elimination of this patient tended to be rather high on the usual diet, which we gave during the test, we repeated the test with the patient on a milk and toast diet. Even then he still eliminated about 120 mg. of free benzoic acid in twenty-four hours. Only after he had been on this diet for five days, did the urine become practically free from unconjugated benzoic acid. A preliminary urine sample for six hours contained 0.050 gm. of total benzoic acid and the hippuric acid output was 0.065 gm. The patient was given 2 gm. of benzoic acid in capsules and a second urine sample for six hours was collected.

This time the urine contained 1.648 gm. total benzoic acid. The free benzoic acid rose markedly from 0.006 gm. to 0.130 gm. in the six hours. The hippuric acid output was 2.228 gm. Introducing the proper corrections, we find that 80 per cent. of the ingested benzoic acid was eliminated in six hours, while 74 per cent. of the theoretical amount of hippuric acid was synthesized. A third urine was collected for the next eighteen hours, thus completing the twenty-four hour sample. This last urine contained 0.371 gm. total benzoic acid. The free

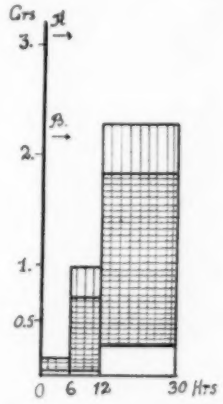

Fig. 15.—Case 11; first test.

benzoic acid diminished greatly and was only 0.087 gm. The hippuric acid output was 0.417 gm. The total elimination for twenty-four hours included, therefore, 91 per cent. of the ingested benzoic acid, and 81 per cent. of the expected hippuric acid synthesis had taken place. It should be noted that about three weeks had elapsed between these two tests and that the patient had developed in the meantime signs of cardiac decompensation.

Case 11.—J. L. P., male, aged 42, was admitted to the University Hospital, April 20, 1922.

History.—Six months ago patient first noticed that he was becoming weak. He has suffered frequent attacks of dizziness, more marked the last six weeks. There has been an increasing amount of urine, and the nocturia has increased in the last four months from one to five or six times. There has been some puffiness about the eyes, but no swelling.

Past Illness.—During childhood whooping cough, chickenpox and measles. Five years ago he had malaria. He gives a history of a chancre in 1907.

Physical Examination.—A well formed and well nourished young man, somewhat pale and with some edema about the eyes. Eyegrounds negative; pupils equal and active; tonsils normal; teeth in poor condition. Cervical glands

barely palpable. Lungs are negative. Heart enlarged, both second sounds markedly accentuated. Blood pressure, 230/140. Abdomen negative. Extremities and reflexes normal.

Laboratory Examination.—Blood: Wassermann test, three plus positive. Red blood cells, 4,350,000; white blood cells, 7,500; hemoglobin, 75 per cent.; 100 c.c. blood contained 132 mg. sugar, 89 mg. nonprotein nitrogen, 8.3 mg. uric acid.

Diagnosis.—Chronic diffuse nephritis.

Tests of Kidney Function: Phenolsulphonephthalein output in two hours and ten minutes, 9 per cent.

Hippuric Acid Test: First test: This was made soon after patient was admitted to the hospital. For two days previous to the test he was on a milk and toast diet. A six hour preliminary urine sample contained 0.146 gm. of total benzoic acid. Unfortunately, the free benzoic acid determination was not successful, but it was approximately 0.046 gm. There was, therefore, 0.148 gm. hippuric acid. The patient took 2 gm. benzoic acid in capsules. In the next six hours his urine showed 0.702 gm. of benzoic acid (0.037 gm. unconjugated)

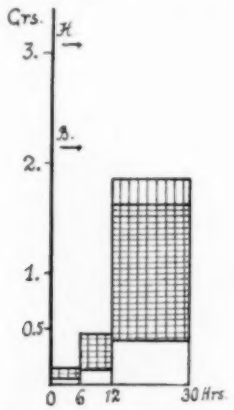

Fig. 16.—Case 11; second test.

and 0.976 gm. of hippuric acid. He, therefore, excreted 33 per cent. of the administered benzoic acid and synthesized 28 per cent. of the theoretical amount of hippuric acid. In the next eighteen hours, however, his urine contained 1.815 gm. of benzoic acid. The amount of unconjugated acid increased to 0.259 gm. The hippuric acid output was 2.282 gm. In twenty-four hours following the benzoic acid ingestion—making proper allowance for the normal elimination—the patient excreted 100 per cent., or the full dose of the benzoic acid, and 91 per cent. of the possible synthesis into hippuric acid occurred in that time. The results with this patient are essentially the same as obtained in the previous two cases, except that the rate of excretion was much slower.

Soon after the first test the patient's condition began to grow worse. He developed albuminuric retinitis, severe headaches, etc. A second test was made on him ten days later, four days before he died of uremic coma.

Second Test: The preliminary six hour urine contained 0.153 gm. benzoic acid with 0.050 gm. as the unconjugated acid. The hippuric acid output was, therefore, 0.152 gm. It is interesting to observe that in spite of the fact that the patient had been limited to a diet as nearly as possible poor in benzoic acid, he continued to excrete relatively large amounts of free benzoic acid and we never succeeded in his case to lower the free benzoic acid excretion to the

point where it would be entirely negligible for the hippuric acid calculation. After administering 2 gm. of benzoic acid in gelatin capsules a second six hour urine was collected, which contained only 0.615 gm. total benzoic acid. The free benzoic acid increased to 0.192 gm., i. e., almost fourfold over that of the preliminary period, and the hippuric acid output was 0.620 gm. In this test only 23 per cent. of the total benzoic acid ingested and 16 per cent. of the possible hippuric acid were recovered in six hours, a considerable reduction since the previous test. The third urine for the next eighteen hours contained 1.620 gm. total benzoic acid with a large amount (0.361 gm.) in the unconjugated state, so that only 1.847 gm. hippuric acid was excreted. It is to be noted and will be seen clearly from the charts, that the course of the benzoic and hippuric acid excretion is similar in both tests, except that in the second test, made three days before the onset of uremia, which led to coma, and soon terminated in death, only 81 per cent. of the administered benzoic acid was recovered in the twenty-four hour urine, while of the theoretic amount of hippuric acid only 63 per cent. was actually synthesized.

With the onset of the comatose condition, the composition of the blood showed unmistakeable evidence of its uremic nature. Two samples of blood obtained thirty hours before death and soon after death occurred (taken directly from the heart) had the following composition:

100 C.c. Blood Contained:	First Blood, Mg.	Second Blood, Mg.
Sugar	139	162
Nonprotein nitrogen	223	253
Urea	166	193
Uric acid	11.3	15.6
Creatinin	12.6	13.3
Creatin	...	8.4

NECROPSY REPORT

Dr. J. Jay Keegan reports as follows on the necropsy:

The necropsy findings were essentially negative except in the kidneys and heart. The kidneys were slightly smaller than normal. The capsule stripped easily leaving a finely granular and mottled surface. The cortex was distinctly thinned, measuring less than 5 mm. in thickness in most regions. There was not clear distinction between cortex and medulla. The entire cut surface was mottled with red and gray. There was increased resistance to section. Microscopically, the chief lesion appeared in the interstitial tissue and in the blood vessels. There was a rather patchy increase of dense fibrous interstitial tissue without inflammatory cell infiltration, and the arterioles in all regions showed a marked thickening of the entire wall, with frequent hyaline degeneration and occlusion of the lumen. There was no cellular infiltration of the vessel walls and no marked hyperplasia of the intima. There was a moderate hyperplasia of the endothelium of the glomerular capillaries, but no inflammatory cell infiltration. Hyaline degeneration was frequent and occasionally there appeared ruptured capillaries with hemorrhage into Bowman's capsule and into the proximal convoluted tubules. Bowman's capsule was not thickened and the glomerular tuft not unduly lobulated. The pathology in the kidney is interpreted as chiefly vascular and interstitial rather than inflammatory, glomerular or tubular. The changes in the entire kidney might be interpreted as primarily vascular, but as in all such cases the value of the deduction would be questionable.

The heart showed a marked hypertrophy of the left ventricle, normal valves, and a few degenerated intimal plaques in the ascending aorta.

Sections of the liver showed nothing abnormal in this organ.

The results which we discussed in detail in the foregoing pages are summarized in the accompanying table.

The study of the hippuric acid synthesis which we carried out with several normal and pathologic subjects leads us to the following considerations. In the tests with normal subjects we found that the addition of benzoic acid, calling on the kidney for an increased effort, has evidently a stimulating action on that organ. In our tests we not only recovered in twenty-four hours the full amount ingested but an appreciable excess, and, furthermore, the hippuric acid elimination, even in the next twenty-four hours, exceeded that found during the fore-period. In the pathologic subjects this is quite different. Here the ingestion of an extra amount of benzoic acid or its salt led to an output of benzoic acid or of its conjugation product—hipurric acid, more or less below the expected quantity. Besides, the excretion of both total benzoic and hippuric acid for the second twenty-four hour period after the ingestion (i. e., from twenty-four to forty-eight hours later) was less than in the preliminary period. It seems, therefore, probable that the pathologic kidney not only fails to accomplish the task of synthesis imposed on it, but in the effort it actually becomes partially exhausted or fatigued.

The elimination of benzoic acid or of its salts from the body follows very rapidly. Appreciable quantities are excreted within six hours and even in the pathological cases the largest amount may pass through the kidney in the first few hours. It is remarkable that on diets very poor in benzoic acid content the hippuric acid output in the urine remains relatively high. Benzoic acid must be, therefore, continually produced in the intestine and absorbed into the circulation. Kingsbury and Swanson [18] found the daily excretion of about 1.7 gm. hippuric acid in a normal person on a mixed diet. When the diet was changed to one consisting of milk, cream, cheese, rock candy, i. e., one eminently poor in benzoic acid, the hippuric acid output diminished to about 0.7 gm. but the significant thing is that for forty-eight hours after the change had been made the hippuric acid excretion still remained quite high. In at least two of our patients (Cases 10 and 11) with persistent constipation, we found it rather difficult to reduce the benzoic acid output by a restriction to a diet of milk and toast. We found it necessary to give this diet for forty-eight hours preceding the test, but even then the urine in Case 11 with the more pronounced and severe intestinal trouble could not be made entirely free from unconjugated benzoic acid. The experience with our patients has suggested the possibility that intestinal putrefaction may in some way be associated with hippuric acid elimination, and particularly with the free benzoic acid in the urine. Weyl and Anrep [9] noted in febrile animals that the proportion of free benzoic acid increases in that condition, and, further-

RESULTS OF ANALYSIS MADE ON EIGHT PATIENTS

No. of Case	Clinical Diagnosis	Blood (Mg. per 100 C.c.)			Urine			Tests of Kidney Function			Remarks
									Hippuric Acid Test		
		Sugar	N.P.N.	Uric Acid	Daily Output, C.c.	Average Specific Gravity	Albumin per Cent.	Phenolsulphonephthalein, per Cent.	Per Cent. of Benzoic Acid Recovered	Per Cent. of Hippuric Acid Recovered	
4	Subacute diffuse nephritis	91	48	1.8	800	1.024	++++	45	77	76	2.4 gm. sodium benzoate administered in water. Benzoic and hippuric acid determined in 24 hour urine
5	Cardiorenal with albuminuric retinitis	120	65	4.5	2,500	1.010	0.08	15	59	58	2.4 gm. sodium benzoate administered in water. Benzoic and hippuric acid determined in 24 hour urine
6	Cardiorenal	100	61	4.5	1,020	1.013	0.12	40	88	83	2.4 gm. sodium benzoate administered in water. Benzoic and hippuric acid determined in 24 hour urine
					520	1.017	....		77	62	2.0 gm. benzoic acid administered in capsules. Benzoic and hippuric acid determined in 24 hour urine
					380	1.014	....		\15 /56	\14 /50	2 gm. benzoic acid given in capsules. Benzoic and hippuric acid determined after 6 and 24 hours. Milk and toast diet
7	Chronic interstitial nephritis	98	117	6.5	1,200	.....	....	10	76	72	2.4 gm. sodium benzoate administered in water. Benzoic and hippuric acid determined in 24 hour urine
					1,820	1.008	0.4		\55 /77	\65 /70	1.2 gm. sodium benzoate administered on two consecutive days. Benzoic and hippuric acid determined in 24 hour urines
8	Cardiorenal	110	48	...	780	1.014	+	50	67	53	2.4 gm. sodium benzoate administered in water. Benzoic and hippuric acid determined in 24 hour urine
					820	1.017	+		87	79	2 gm. benzoic acid given in capsules. Benzoic and hippuric acid determined in 24 hour urine
					1,800	1.010	+		\84 /84	\73 /71	2 gm. benzoic acid given and determinations made on 6 and 24 hour urine. Exclusive milk and toast diet
9	Chronic diffuse nephritis	98	74	5.4	1,340	1.012	0.2	15	96	74	2.4 gm. sodium benzoate administered in water. Benzoic and hippuric acid determined in 24 hour urine
10	Cardiorenal	109	56	4.8	2,900	1.006	0.18	35	\ 81 /100	\76 /95	2 gm. benzoic acid given in capsules. Benzoic and hippuric acid determined in 6 and 24 hour urine. Milk and toast diet
					2,200	1.009	....		\80 /91	\74 /81	2 gm. benzoic acid given in capsules. Benzoic and hippuric acid determined in 6 and 24 hour urine. Milk and toast diet
11	Chronic diffuse nephritis	132	89	8.3	2,450	1.011	0.16	9	\ 33 /100	\28 /91	2 gm. benzoic acid given in capsules. Determinations made in 6 and 24 hour urine. Milk and toast diet
					2,250	1.010	....		\23 /81	\16 /63	2 gm. benzoic acid given in capsules. Determinations made in 6 and 24 hour urine. Milk and toast diet

more, that the excess of unconjugated benzoic acid was not due to a lack of glycocol as it did not diminish upon the addition of glycocol to the food. In all of our patients except one (Case 5) the free benzoic acid in the urine following ingestion of benzoic acid or its salt increased markedly. We believe this to be the reason why Kingsbury and Swanson [18] thought the hippuric acid synthesis to be complete in nephritics, because they did not actually determine the free benzoic acid, regarding it a negligible quantity and assuming that it will not vary from the normal after the absorption of a large dose of the acid or its salt. Our analyses give no support to this assumption, and, as was already pointed out previously, their conclusion applies only to the total benzoic acid output in the urine, and not to the hippuric acid synthesis. In this connection it is well to note that in several of our patients (Cases 9, 10 and 11) the complete amount, or very nearly so, of the benzoic acid administered was recovered in twenty-four hours, while only from 63 to 95 per cent. of the possible hippuric acid was synthesized in the same time. It is not improbable that Kingsbury and Swanson's patients were also of this type. This may explain why they recover practically 100 per cent. of the administered benzoic acid, except that it is erroneous to identify all of this with its conjugation product, the hippuric acid.

Surveying the results with the patients under our observation we are inclined to believe that the elimination of free benzoic acid has been particularly marked in the nephritics and to a less extent in the cardiorenal cases. We appreciate, of course, that a larger number of patients would have to be examined before this could be definitely established.

Before leaving the subject of the free benzoic acid in the urine we wish to relate one particular instance, because we realize that criticism would be directed most vigorously against these results. One of us (S. M.) had taken the usual dose of benzoic acid but for some undiscoverable reason he experienced great discomfort shortly afterward. There was a strong burning sensation in the bladder and also during micturition. Although practically the full amount of benzoic acid consumed was eliminated in six hours, the free benzoic acid portion increased from 0.024 gm. in the preliminary urine to 0.256 gm. in the next six hours and most of this was passed soon after the benzoic was taken. The urine was intensely acid, and judging by the burning sensation and by the fact that the membrane of the bladder was so severely irritated that the urine was full of mucous shreds (there was no albumin), this must have been due to benzoic acid and not its salts. We have not been able to find out the cause of the disturbance which this test occasioned, especially as the other tests performed with the same subject were free from all unpleasant accompaniments. In fact, the test repeated a few days later was very successful and none of the symptoms described above occurred.

Another point which should be noted is that the patients arrange themselves into two groups as regards the elimination of benzoic acid: in one group (Cases 9, 10 and 11) from 74 to 95 per cent. is synthesized to hippuric acid in twenty-four hours, while the entire amount, or nearly so, of the administered benzoic acid appears in the urine; in the other group (Cases 4 to 8) from 59 to 88 per cent. of the benzoic acid ingested has been recovered. Since we followed the benzoic and hippuric acid elimination in the urine for forty-eight hours after the administration of the benzoic acid, we are certain that this is not simply due to delayed excretion in these patients. The fact that the full amount of benzoic acid was not recovered would naturally lead one to suppose that either a part of the ingested benzoic acid has been conjugated in some other form, for instance, as a glucosid with glycuronic acid or in some other form and thus escaped detection. Dakin,[24] even when from 5 to 6 gm. of sodium benzoate was given several days in succession, found no evidence that the benzoic acid undergoes oxidation, and he found only trifling amounts of glycuronic acid derivatives in the urine. It is possible, of course, that a process which in the normal organism is of slight significance may assume much greater importance under pathological circumstances. Unfortunately, we did not attempt to solve this problem by direct experimentation and can therefore offer no valid data at present for the elucidation of this point.

GENERAL CONCLUSIONS AND SUMMARY

In normal persons benzoic acid, administered either as the acid or its salt is completely synthesized to hippuric acid and the kidney is stimulated to enhanced activity. In nephritic and cardiorenal patients the synthesis is never complete and the kidney is apparently fatigued by the excessive exertion.

The benzoic acid passing in the urine is not all conjugated with glycocol to form hippuric acid. A variable portion appears as the uncombined acid or as its salts. The unconjugated part of the benzoic acid can be reduced to an entirely negligible amount on a diet of milk and toast. Following the ingestion of a large dose of benzoic acid or sodium benzoate the free benzoic acid in the urine invariably increases, though to a very variable degree in different individuals. The increase is particularly great in patients with a definite kidney affection.

In all the patients which we examined the per cent. of hippuric acid synthesized in twenty-four hours, following the ingestion of a standard dose of benzoic acid or sodium benzoate, ranged from 53 to 95 per cent., while from 59 to 100 per cent. of the benzoic acid administered

24. Dakin, H. D.: The Fate of Sodium Benzoate in the Human Organism, J. Biol. Chem. **7**:103, 1910.

could be recovered in the urine. In one group of patients, the recovery of benzoic acid has been almost the same as in normal subjects, but the hippuric acid synthesis was less than in the normal owing to the fact that a large amount of the benzoic acid was excreted in unconjugated form. In another group of patients both the elimination of total benzoic and of hippuric acid falls much below that in the normal subject. The free benzoic acid in the urine following a dose of the acid is apparently greater in the nephritic than in the cardiorenal cases.

Clinically, the method will in all probability not find extensive application or favor because it involves much work, and in order to secure reliable results the patient's regimen must be supervised very closely. Besides, the determinations require the strict care and precaution of the usual quantitative chemical analysis, a condition which the ordinary clinical laboratory does not satisfy. The test carried out with the same patient does not always yield quantitatively similar results which makes their proper interpretation still more difficult.

In conjunction with other renal function tests, the hippuric acid synthesis and the elimination of the benzoic acid may serve a very useful purpose. From our long experience with the method we would suggest that in performing the test for diagnostic purposes the following routine procedure should be observed. The patient should be on an exclusive diet of milk, cream, cheese, sugar with a liberal allowance of water, at least one day before the test is made. The patient should pass urine immediately before the substance is administered. It is preferable to give the necessary dose (2 gm. benzoic acid or 2.4 gm. sodium benzoate) in gelatine capsules as this eliminates any loss through incomplete solution or possible spilling when the solution is taken by the patient, especially when he is in a reclining position in bed. The urine collected for six hours after the substance had been taken should be analyzed according to the method described in the beginning of the paper for both the free and conjugated benzoic acid (hippuric). A second urine sample for eighteen hours should also be collected, thus completing a twenty-four hour urine after the benzoic administration, and analyzed in the same way. Alkalinization should be discontinued for the period of the test to prevent the possibility of the urine becoming alkaline. The urine samples should be properly preserved with thymol and kept in a cool place before analyzed. A general correction of 0.2 gm. hippuric and 0.14 gm. benzoic acid for every six hours may be applied and the amount of benzoic and hippuric acid recovered in the six and in the twenty-four hour period calculated from the experimental data.

It gives us great pleasure to express our appreciation to the staff of the medical ward of the University Hospital for their faithful and friendly cooperation. We are particularly indebted to Dr. J. Jay Keegan for his unremitting interest in the work and the many courtesies so generously extended to us.

EDEMA ASSOCIATED WITH MODERATE BICARBONATE ADMINISTRATION DURING CONVALESCENCE FROM PNEUMONIA *

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Sellards [1] showed that in normal persons the administration of from 5 to 10 gm. sodium bicarbonate is sufficient to turn urine alkaline, while in patients suffering from acidosis a greater amount is required. Indeed, Palmer reports patients suffering from uremia who received 112 gm. sodium bicarbonate and still excreted acid urine. Further investigations by Palmer and Van Slyke [2] demonstrated that in normal men the urine becomes more alkaline than the blood ($p_H = 7.4$) when the plasma bicarbonate exceeds 71 ± 5 volumes per cent. Of the ten pathologic cases which they studied during sodium bicarbonate administration, most showed a higher plasma bicarbonate level than this, before the urine became more alkaline than the blood. They conclude, therefore, that in pathologic conditions there is danger of giving "unnecessary and perhaps injurious" amounts of sodium bicarbonate if administration is continued until the urine turns alkaline; and that the administration should be discontinued when the blood bicarbonate becomes normal.

The case which we are here describing is one in which after administration of sodium bicarbonate in amounts of from 5 to 6 gm. per day for several weeks, an alkali excess in the blood was observed, despite a continuously acid urine. The bicarbonate retention was accompanied by a water retention of 11 kilograms with an edema which involved the lungs and appeared to be responsible for abnormalities of clinical importance in the respiration (rapid, very shallow breathing, and intense cyanosis). Bicarbonate administration was stopped, and the patient was kept in an atmosphere with 40 per cent. of oxygen to relieve the anoxemia. The kidneys began almost at once to excrete bicarbonate, the edema gradually disappeared, and the respiration became normal.

REPORT OF CASE

History.—A married woman, aged 47 years, had with the exception of frequent attacks of sinus infections, for the past several years enjoyed good health.

* From the Hospital of the Rockefeller Institute for Medical Research.

1. Sellards, A. W.: Johns Hopkins Hosp. Bull. **23**:289, 1912.

2. Palmer, W. W., and Henderson, L. J.: Arch. Int. Med. (Aug.) **12**:153, 1913; Palmer, W. W., and Van Slyke, D. D.: J. Biol. Chem. **32**:499, 1917.

She had noticed, however, that for almost six years slight exertion caused shortness of breath. Feb. 17, 1922, while on the train en route to New York, she had a chill. Two days later she was confined to bed in a New York hotel with a temperature of 102 F. and respirations of 30 to the minute. The following day there were râles in the left lower chest, pain on deep breathing, and blood tinged sputum, from which pneumococcus Type I was isolated. The condition thereupon ran the course of a lobar pneumonia with areas of consolidation in the upper halves of both lower lobes. February 26, a heavy trace of albumin was noted in the urine, but no casts were seen. During the critical part of her illness, there was well marked cyanosis, and respirations were shallow and reached 60 per minute.

Course.—After having had 1,000 c.c. of antipneumococcus serum, her temperature gradually fell, and remained between 100 and 101 F., her respirations at 40 per minute. March 20, or a little more than a month after the onset of the acute illness, moderate edema of the left foot and ankle appeared. Beginning about March 24, the patient did not seem so well, the cyanosis increased, the urinary output diminished, and gereneralized edema of the body appeared, respirations were shallow, and the patient was slightly irrational. There was a heavy trace of albumin in the urine which was acid to litmus and contained many hyaline and granular casts. This condition persisted for the following five days, when the patient was first seen by one of us.

TABLE 1.—OXYGEN AND CARBON DIOXID CONTENT OF BLOOD AND p_H OF PLASMA AND URINE

Arterial Whole Blood							
Oxygen Content, Volume per Cent.	Oxygen Capacity, Volume per Cent.	Oxygen Unsaturation		Carbon Dioxid Content		Plasma, p_H	Urine, p_H
		Volume per Cent.	Per Cent. of Capacity	Total, Volume per Cent.	Bicarbonate, Millimolecular		
8.24	13.49	5.25	39	70.6	30.0	17.49	6.2

Treatment.—She was admitted to the Hospital of the Rockefeller Institute for the purpose of investigating the cause of her cyanosis and dyspnea. The patient was put on a Gatch bed in a fairly upright position, which somewhat relieved her respiratory distress. The fluid intake was restricted to 1 liter per day, and she was given a salt-free diet. No medication was prescribed. The following day, blood was drawn from the radial artery and analyzed for its oxygen and carbon dioxid content, and the plasma p_H. The results of this analysis are shown in Table 1.

Discussion.—The oxygen figures indicated an oxygen unsaturation in the arterial blood sufficient to account for the cyanosis. Lundsgaard [3] has shown that when the average capillary unsaturation, estimated as the mean between the arterial and venous exceeds about 6.5 volumes per cent. of oxygen, cyanosis usually becomes visible. We were not able to obtain venous blood from this patient, because of her extensive edema, but with a normal fall of 5 volumes per cent. from arterial to venous oxygen, the mean capillary unsaturation would be $5.25 + 2.5 = 7.75$ volumes per cent.

The bicarbonate concentration of 30 millimolecular in the whole blood as drawn was 50 per cent. above the normal average of 20

3. Lundsgaard, C.: J. Exper. M. **30**:259, 1919.

millimolecuar for blood with p_H 7.49.[4] The p_H of 7.49,[5] though not certainly above extreme normal range, was near the upper extreme. The condition of the acid-base balance was, therefore, one of alkali excess, or bicarbonate retention. The acid urine (p_H 6.2) indicated a pathologic inability to excrete the bicarbonate.

Since alkali excess can hardly occur in man without alkali administration, inquiry was made concerning previous alkali therapy, and it was ascertained that during the thirty-five days of her illness prior to admission to the hospital, she had been given approximately 200 gm. sodium bicarbonate, or on an average of 5.7 gm. per day, not in itself an excessive dose. All the while the patient had been excreting a urine acid to litmus.

Oxygen Therapy.—Because of the pronounced arterial unsaturation, oxygen therapy seemed indicated. Accordingly the patient was put in the oxygen chamber and exposed to an atmosphere containing 40 per cent. of oxygen. Relief from symptoms was immediate and striking. Cyanosis disappeared, and the respiratory rate fell. At the time of admission to the chamber the chief physical signs and symptoms were intense cyanosis, rapid breathing, generalized anasarca and hydrothorax. After twenty-four hours in the oxygen chamber, the patient was removed for the purpose of getting a roentgenogram of her chest. The recurrence of cyanosis and subjective discomfort were as prompt and striking as their disappearance had been, and on return to the chamber they again vanished.

Table 2 gives the blood gas analyses and the pulmonary ventilation on four successive days, the first and third with the patient breathing atmospheric air, the second and fourth with the patient breathing an atmosphere containing twice the normal oxygen concentration. The subsequent findings during convalescence are also brought out in this table.

In both instances of exposure to 40 per cent. oxygen, the minute volume of pulmonary ventilation diminished, due to a fall in the respiratory rate, the depth of individual respirations (tidal air) remaining unchanged. In both instances the arterial unsaturation disappeared, and in both instances there was a marked diuresis. Whether this diuresis was real, due to an improved oxygenation of kidney tissue, or whether it was apparent and due to a lessened water elimination through the lungs consequent to the diminished minute volume of pulmonary ventilation, we cannot be sure.

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4. Van Slyke, D. D.: J. Biol. Chem. **49**:158, 1921 (Fig. 2).

5. The blood p_H examinations were made by the method recently described by Cullen and checked electrometrically.

TABLE 2.—Showing Data as to Respiration, Arterial Blood and Urine

Date	Day of Disease	Respiration: Respirations per Min.	Minute Volume, Liters	Tidal Air, C.c.	Residual Air, Liters	Vital Capacity, Liters	Lung, Total Capacity, Liters	Arterial Blood: Oxygen Content, Volume per Cent.	Oxygen Capacity, Volume per Cent.	Unsaturated: Volume per Cent.	Unsaturated: Per Cent. of Capacity	Carbon Dioxid Content, Volume per Cent.	Ps	Urine: Fluid Intake, C.c.	Fluid Output, C.c.	Reaction to Litmus	Ps	Estimated $NaHCO_3$ Output, Gm.	Body Weight in Kilos	Inspired Air, per Cent. Oxygen
March 30	40	46	8.06	176	....	....	....	8.24	13.49	5.25	39	70.6	7.49	905	670	Acid	...	...	69.6	21
March 31	41	32	5.53	170	....	....	....	14.40	14.30	0	0	81.0	7.55	805	1,490	Acid	6.2	0.3	67.0	40
April 1	42	46	8.14	178	....	....	....	10.91	14.30*	3.39	24	78.3	7.52	1,000	790	Alkaline	...	...	66.7	21
April 3	44	24	4.49	184	....	....	....	13.90	14.20	0.30	2.1	77.1	7.45	880	1,753	Alkaline	7.9	13.5	65.5	40
April 6	47	37	8.73	234	....	0.64	....	.....	.....	....	..	....	....	1 000	2,095	Alkaline	...	...	62.8	21
April 8	49	22	6.30	293	0.50	0.88	1.48	.....	.....	....	..	....	....	1 000	1,560	Alkaline	...	...	62.0	21
April 13	54	20	8.65	430	1.00	1.07	2.07	.....	.....	....	..	....	....	1,000	931	Acid	...	...	58.6	21
April 19	60	..	....	....	....	....	....	14.35	15.65	1.30	8.3	52.3	7.49	1 000	1.145	Acid	...	...	58.6	21
April 29	70	..	....	...	....	....	....	.....	.....	....	..	....	....	1,500	1.055	Acid	5.4	0 03		
May 9	81	20	10.88	538	0.98	1.52	2.50	.....	.....	....	..	....	....	.....	.....	.....	...	...	....	21
May 10	82	..	.....	...	....	....	....	13.01	13.56	0.55	4.0	50.6	7.45	.....	.....	.....	...	...	....	21
May 12	84	20	10.50	540	1.10	1.00	2.70	.....	.....	....	..	....	....	.....	.....	.....	...	...	....	21

* Assumed.

Loss of Edema.—The patient was kept in the oxygen chamber continuously for the five days following April 1. April 6 she was removed, when cyanosis no longer persisted under atmospheric conditions. During this time her weight fell from 69.6 kilos to 62.9 kilos; her twenty-four hour fluid excretion often more than doubling her intake. Tissue edema rapidly decreased. April 1 her urine, which had been acid to litmus and contained many casts, became alkaline and no casts were to be seen. It remained alkaline to litmus until April 9, when it again became acid without a recurrent appearance of casts. The hydrogen ion concentration of the urine is shown in Table 2. Progressive loss of weight continued until April 12, when the weight curve became flat and the patient was apparently in water balance.

With the disappearance of fluid from the chest, the tidal air gradually increased, and the patient's lung volume, which had been much reduced, due no doubt to compression of the lungs by hydrothorax, and to pulmonary edema, also augmented as shown in Table 2.

TABLE 3.—Results of Renal Function Tests with Normal Values Shown

	Observed	Normal
Blood urea nitrogen, gm. per liter	0.0625	0.15-0.25
Urea index (Austin, Stillman and Van Slyke)	53	45-115
Plasma chlorids, gm. per liter	5.76	5.62-6.20
Plasma proteins:		
Albumin, per cent.	3.9	5.0
Globulin, per cent.	3.7	3.0
Total protein, per cent.	7.6	8.0
Globulin ÷ Total protein	48	30
Phthalein, 1st hour per cent.	34	
Phthalein, 2d hour per cent.	14	
Total per cent.	48	60-80

Kidney Function.—An effort to account for the alkali retention in this case on the basis of renal insufficiency was made by a study of the patient's renal function, which was done on April 19 by Dr. Geoffry Linder of the Staff of the Rockefeller Hospital. In summary, it may be said that the phthalein excretion showed a value below normal; and the plasma globulin formed a somewhat higher proportion of the total protein than normal, as frequently seen in cases of nephritis with edema and albuminuria. The renal functional tests made are given in Table 3 with accompanying normal values.

The dilution and concentration test showed a normal water excreting function.

Disappearance of Alkalosis.—Examination of the arterial blood carbon dioxid content and p_H values shown in Table 2, reveals some interesting facts. The 70.6 volume per cent. carbon dioxid at the time of admission increased during the next day to 81.0 volumes per cent. This was accompanied by an increase in p_H from 7.49 to 7.55, and

signifies, we believe, a transport of base from the tissues to the blood. The next two observations show a drop in carbon dioxid volume per cent. to 78.3 and 77.1 successively, and in p_H to 7.52 and 7.45. Just at this time the urinary p_H [6] which had been 6.2 became 7.9, indicating the passage of retained base from the blood stream through the kidneys. This change was accompanied by the enormous loss of tissue edema mentioned above. Assuming the urinary unbound carbon dioxid to be 4.2 volumes per cent., Gamble [7] has calculated the bicarbonate content of urine from the p_H. A rise such as this from p_H 6.2 to p_H 7.9 represents an increase in sodium bicarbonate elimination from approximately 0.2 gm. per liter to 8 gm. per liter.

Apparently when the body retains bicarbonate, it retains sufficient fluid to keep the osmotic concentration in body fluids normal. With cessation of bicarbonate administration and improvement of kidney function, in this case, fluid and base were eliminated simultaneously. It is possible that the relief from anoxemia was in some degree responsible for the improved kidney function.

SUMMARY AND CONCLUSIONS

The case studied was one of lobar pneumonia, in which an average of 5.7 gm. sodium bicarbonate had been given for a period of thirty-five days prior to admission to the hospital. The patient showed intense cyanosis with marked oxygen unsaturation of the arterial blood, rapid breathing, anasarca and hydrothorax, and evidence of alkalosis (blood p_H 7.55). Oxygen therapy largely relieved cyanosis and dyspnea. Immediately thereafter the patient began to excrete retained base and water. Whether this was more than a coincident relationship and just what rôle the salt free diet played in dehydration we are unprepared to say. Diminution of edema was accompanied by gradually increasing lung volume and return to normal type of respiration. No definite impairment of kidney function could be established other than shown by a slightly reduced phthalein excretion. At the time of discharge from the hospital, the patient's blood oxygen, carbon dioxid content, and p_H were normal, the urine p_H was normal, and the urine was free from albumin and casts. The case is reported to show that definite untoward results may follow the administration of sodium bicarbonate, and to point out the character of certain of these untoward results.

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6. The urine was collected without precaution against exposure to air and colorimetric hydrogen ion concentration determinations made on freshly voided specimens.

7. Gamble, J. L.: J. Biol. Chem., **51**:295, 1922.